Rapid Sequence Intubation by Paramedics in Out-of-hospital Non-traumatic Brain Pathologies

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A thesis submitted for the degree of Doctor of Philosophy

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Melbourne, Australia

March 2020

Contents

General Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes five original papers submitted for publication in peer-reviewed journals. Its core theme is the utility of paramedic rapid sequence intubation (RSI) in non-traumatic brain pathologies (NTBP). The ideas, development and writing up of all the papers included were the principal responsibility of myself (the student), working within the Department of Community Emergency Health and Paramedic Practice at the School of Primary Health Care, Faculty of Medicine, Nursing and Health Sciences at Monash University, under the primary supervision of Dr Paul Andrew Jennings. The inclusion of co-authors reflects that the work derives from active collaboration between researchers and acknowledges input from team-based research. In the case of five chapters and four publications, my contribution to the work is outlined in Table A1.

Table A1: Contribution to the Work

Publication title	Status	Nature and % of student contribution	Co-author name(s), nature and % of co-author's contribution*	Co-author(s), Monash student Y/N*
Emergency endotracheal intubation in non-traumatic brain pathologies: A systematic review and meta-analysis	Published in *Emergency Medicine Australasia*	85%. Conception, data collection, statistical analysis and writing of manuscript	Paul Jennings, Chris Stein, Karen Smith, Malcolm Boyle and Stephen Bernard assisted with manuscript preparation ≈ 10%. Chris Stein assisted with quality rating ≈ 5%	No
Survival in out-of-hospital rapid	Published in *Prehospital*	85%. Conception, data	Paul Jennings, Karen Smith, Malcolm Boyle	No

sequence intubation of non-traumatic brain pathologies	*Emergency Care*	collection, statistical analysis and writing of manuscript	and Stephen Bernard assisted with manuscript preparation ≈ 10%. Karen Smith assisted with data collection ≈ 5%	
The association of paramedic rapid sequence intubation and survival in out-of-hospital stroke	Published in *Emergency Medicine Journal*	85%. Conception, data collection, statistical analysis and writing of manuscript	Paul Jennings, Karen Smith, Malcolm Boyle and Stephen Bernard assisted with manuscript preparation ≈ 10%. Karen Smith assisted with data collection ≈ 5%	No
The Association of Blood-pressure Changes with Survival after Paramedic Rapid Sequence Intubation in Out-of-Hospital Stroke	Under review at *Emergency Medicine Australasia*	85%. Conception, data collection, statistical analysis and writing of manuscript	Paul Jennings, Karen Smith, Malcolm Boyle and Stephen Bernard assisted with manuscript preparation ≈ 10%. Karen Smith assisted with data collection ≈ 5%	No
The Utility of the Brain Trauma evidence to inform paramedic rapid sequence intubation in out-of-hospital stroke	Published in *BMC Emergency Medicine*	85%. Conception, data collection, statistical analysis and writing of manuscript	Paul Jennings, Karen Smith, Malcolm Boyle and Stephen Bernard assisted with manuscript preparation ≈ 10%. Karen Smith assisted with data collection ≈ 5%	No

Acknowledgements

I would like to thank my supervisors Paul Jennings, Karen Smith, Malcolm Boyle and Stephen Bernard for the time they took from their busy schedules to provide me with guidance during my PhD. I further extend my gratitude to my wife, Carla, who unselfishly gave me time at the expense of her own. Also, I am indebted to the staff at the Centre for Victorian Data Linkage and Ambulance Victoria (AV) for being instrumental in collating data for the data linkage studies in this thesis.

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List of Abbreviations

ARAS	ascending reticular activating system
AV	Ambulance Victoria
CI	confidence interval
CO_2	carbon dioxide
EMS	emergency medical service
$ETCO_2$	end-tidal CO_2
GCS	Glasgow Coma Scale
MICA	Mobile Intensive Care Ambulance paramedic
NIHSS	National Institutes of Health Stroke Scale
NTBP	non-traumatic brain pathology
OR	odds ratio
RCT	randomised controlled trial
RSI	rapid sequence intubation
TBI	traumatic brain injury

Definitions

Rapid sequence intubation	RSI is a process that utilises sedative and paralytic drugs to facilitate placement of an endotracheal tube.[1,2]
Non-traumatic brain pathology	NTBP is defined as an acquired brain injury (either permanent or transient) that includes brain tumours, meningitis, encephalitis, hypoxic/anoxic brain injury, stroke, arteriovenous malformations, tumours, aneurysms, brain haemorrhage, as well as brain injury due to diabetes, seizures and toxicity, metabolic conditions, and alcohol and drug overdose.[3]
Traumatic brain injury	Traumatic brain injury (TBI) is a nondegenerative, noncongenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairment of cognitive, physical and psychosocial functions, with an associated diminished or altered state of consciousness.[4]
Ischaemic stroke	Ischaemic stroke occurs when a blood vessel supplying blood to the brain is obstructed and an acute neurologic deficit lasting > 24 hours is present.[5]
Haemorrhagic stroke	Haemorrhagic stroke is a stroke caused by the rupture of a blood vessel in or on the surface of the brain with bleeding into the surrounding tissue, with an acute neurologic deficit lasting > 24 hours.[5]
Observational study	Observational studies draw from samples inference to a population in which the independent variable is not under the

	researcher's control due to ethical concerns or logistical constraints.[6]
Randomised controlled trial	A study in which people are allocated at random (by chance alone) to receive one or several clinical interventions. One of these interventions is the standard of comparison or control.[6]
Survival-to-hospital discharge	Defined as the patient being discharged from hospital alive and is identified from the discharge disposition at hospital separation.[1]

Publications and Presentations

Publications during PhD probation and candidature

1. **Fouche PF**, Smith K, Jennings PA, Boyle M, Bernard S. The association of paramedic rapid sequence intubation and survival in out-of-hospital stroke. *Emerg Med J* [Internet] 2019; **36**(7): 416–22. Available from: https://emj.bmj.com/content/36/7/416.long doi: 10.1136/emermed-2019-208613
2. **Fouche PF**, Carlson JN, Simpson PM. A call to arms for an out-of-hospital advanced versus basic airway trial. Resuscitation [Internet] 2014; **85**(9): e153–4. Available from: https://www.resuscitationjournal.com/article/S0300-9572(14)00504-8/fulltext doi: 10.1016/j.resuscitation.2014.04.018
3. **Fouche PF**, Stein C, Jennings PA, Smith K, Boyle M, Bernard S. Emergency endotracheal intubation in non-traumatic brain pathologies: a systematic review and meta-analysis. *Emerg Med Australas* [Internet] 2019; **31**(4): 533–41. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/1742-6723.13304 doi: 10.1111/1742-6723.13304
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Conference presentations

1. **Fouche PF**. Out-of-hospital RSI in non-traumatic brain pathologies. Oral presentation at: Professionalization of Paramedicine through Research Symposium; ; 2017 Sep 25–26; Melbourne.
2. **Fouche PF**. The utility of the brain trauma evidence to inform paramedic rapid sequence intubation in out-of-hospital stroke. Oral presentation at: Paramedicine Research Symposium; 2019 Nov 25–26; Frankston.

Abstract

Non-traumatic brain pathologies (NTBP) are acquired brain injuries that form a substantial proportion of presentations to emergency departments and emergency services. Examples of these pathologies include brain tumours, meningitis, encephalitis, hypoxic/anoxic brain injury, stroke, arteriovenous malformations, tumours, aneurysms, brain haemorrhage, as well as brain injury due to diabetes, seizures and toxicity, metabolic conditions, and alcohol and drug overdose. NTBPs are a frequent cause of coma, which compromises the patient airway and one's ability to exchange gases in respiration.

Endotracheal intubation techniques such as rapid sequence intubation (RSI) are frequently used to manage the airways of NTBP. A type of intubation that is preceded by drugs that sedate and paralyse the patient, it is not known how common RSI is in those with NTBP or how prevalent such pathologies are in patients that receive the treatment. It is also unclear whether RSI leads to better survival in NTBP and whether the evidence on RSI in brain trauma can be applied to NTBP such as strokes and seizures.

This thesis, which comprises published works, begins by quantifying how common RSI is in NTBP patients. The systematic review showed that emergency intubation, which is typically RSI, was utilised in 12% of all NTBP cases in the published literature. Relatedly, and in the second study of this thesis, it was revealed that in a cohort of paramedic RSI, NTBP formed 58% of all intubations. Therefore, RSI is common in NTBP, and conversely, NTBP are frequent in those that receive RSI. Since the NTBP population receives RSI frequently the importance of good evidence becoming increasingly pressing.

Next, this thesis examined whether RSI is associated with survival for stroke—the most prevalent NTBP treated by paramedics. In a large data-linked propensity-matched cohort study, out-of-hospital RSI by paramedics was associated with decreased survival for intubation in strokes, with an odds ratio (OR) of 0.61 (95% confidence interval [CI] 0.45 to 0.82; $p = 0.001$). Further, this cohort study demonstrated a considerably larger reduction in systolic blood pressure for RSI

recipients compared to no-RSI, with a decrease that was more than twice as large for the latter group. Additional derangements in carbon dioxide (CO_2), oxygen, pulse rate and respiratory rate found here might explain this reduced rate of survival in stroke.

Thereafter, this thesis analysed the full stroke cohort from linked dataset again. The aim of that analysis was to test if the reductions in systolic blood pressure accompanying RSI found in the propensity matched study are indeed associated with poorer survival. Using regression analysis, this study showed that reductions in systolic blood pressure in strokes are not associated with poorer survival. This counter-intuitive finding of no decrease in survival with decreased blood pressure is in concordance with results from in hospital randomized controlled trials (RCT) however. These RCT compared general anaesthesia to conscious sedation in ischemic strokes, and similar to my results, reductions in blood pressure were found with anaesthesia, but with no concomitant increased mortality.

The only RCT evidence to support RSI in both out-of-hospital settings and emergency departments was conducted by Bernard et al. However, this study was directed to TBIs, wherein patients present differently from typical cases of stroke or seizure, and it might follow that this RSI evidence is non-transferable to NTBP. As such, this thesis examines whether the brain trauma evidence can be extrapolated to non-traumatic pathologies. In another large cohort study, the researcher showed that RSI and related factors statistically interact with stroke and TBI, which suggests that intubation affects stroke survival differently from brain injury. Specifically, this analysis found significant interactions in the RSI-only group for age, number of intubation attempts, atropine and fentanyl use, pulse rate and perhaps both scene time and time-to-RSI. Such interactions imply that RSI affects survival differently for TBI versus stroke. If this is the case, then perhaps the TBI evidence cannot be used for stroke RSI.

Finally, it is suggested that progress towards finding a causal link between paramedic RSI and survival in NTBP can be found by employing both observational and experimental study designs. For example, the researcher recommends a pragmatic controlled trial of all RSI, with a subgroup analysis of various clinical conditions. Natural experimental observational designs such as regression

discontinuity and instrumental variables also have their use. A trial remains of primary importance, and this thesis makes a case for such an experiment.

Chapter 1: Description and rationale for this research

1.1 Introduction

1.1.1 What are NTBPs?

Acquired brain injuries are either traumatic or non-traumatic, occur after birth and result in pathological changes in neuronal functioning, affecting the activity, metabolism and physical integrity of neurons.[7-9] Rice et al. define acquired brain injury as 'those instances where an individual sustains damage to the brain sometime after birth … from traumatic or non-traumatic causes'.[7] A leading cause of death worldwide,[9] pathological alterations of neurons due to such trauma can result in mild, moderate or severe disability in areas such as cognition, speech, memory and attention, capacity to reason, abstract thinking, physical function, psychosocial functioning and information processing.[7] These disabilities might cause either transient or permanent disability of functional or psychosocial capacities.[10]

Non-traumatic brain pathologies (NTBP) are a subset of acquired brain injuries that can, similar to traumatic brain injuries (TBI), cause neuronal injury and consequent disability.[7] Non-traumatic brain pathologies are defined as acquired brain injuries (either permanent or transient), and include brain tumours, meningitis, encephalitis, hypoxic/anoxic brain injury, stroke, arteriovenous malformations, tumours, aneurysms, brain haemorrhage, as well as brain injury due to diabetes, seizures and toxicity, metabolic conditions, and alcohol and drug overdose.[9,11,12] This definition excludes any brain injury caused by traumatic means or during the birthing process.[7] Table 1.1 presents a complete list of all ICD10-AM codes for NTBP included in this definition.

Table 1.1: ICD10-AM Codes Used to Practically Define NTBP

Type of NTBI	ICD10-AM codes and description
Haemorrhagic stroke	I60 (subarachnoid haemorrhage)
	I61 (intracerebral haemorrhage)
	P52 (intracranial non-traumatic haemorrhage of fetus and newborn)
	I62.9 (intracranial haemorrhage [non-traumatic], unspecified)
Ischaemic stroke	I63 (cerebral infarction)
	G45 (transient cerebral ischaemic attacks and related syndromes)
Other types of stroke	I64 (stroke not specified as haemorrhage or infarction)
Inflammatory brain diseases	G00 (bacterial meningitis, not elsewhere classified)
	G01 (meningitis in bacterial diseases, classified elsewhere)
	G02 (meningitis in other infectious and parasitic diseases, classified elsewhere)
	G03 (meningitis due to other and unspecified causes)
	A20.3 (plague meningitis)
	A83 (mosquito-born viral encephalitis)
	A84 (tick-born viral encephalitis)
	A85 (other viral encephalitis, not elsewhere classified)
	A81 (atypical viral infections of the central nervous system)
	A87 (viral meningitis)
	B50 (cerebral malaria)
	G04 (encephalitis, myelitis and encephalomyelitis)
	G05 (encephalitis, myelitis and encephalomyelitis in diseases, classified elsewhere)
	G06 (intracranial abscess and granuloma)
	G07 (intracranial and intraspinal abscess and granuloma in diseases, classified elsewhere)
	G08 (intracranial and intraspinal phlebitis and thrombophlebitis)
	B22 (HIV disease resulting in encephalopathy)
Anoxic/hypoxic brain injury	G93.1 (anoxic brain damage)
	G97.8 (brain [non-traumatic] hypoxia, resulting from procedure)
	P20.9 (brain [non-traumatic] hypoxia, anoxic intrauterine and resulting from birth)

	T88.5 (complications resulting from a procedure, anoxic/hypoxic brain damage) P91.6 (hypoxic ischaemic encephalopathy of newborn)
Seizures	G41 (status epilepticus) G40 (epilepsy) F445 (dissociative convulsions) P90 (convulsions of newborn) R56 (convulsions, not elsewhere classified)
Toxicity and toxic encephalopathy	G92 (toxic encephalopathy) T51-T65 (toxic effect of alcohol, organic solvents, etc.) T36-T51 (poisoning by drugs, medicaments and biological substances) X40-X49 (accidental poisoning by and exposure to noxious substances) X60-X69 (intentional self-poisoning)
Neoplasms of brain	C70 (malignant neoplasms of meninges) C71 (malignant neoplasm of the brain) C793 (secondary malignant neoplasm of the brain and cerebral meninges)
Hydrocephalus	G91.0 (communicating hydrocephalus) G91.1 (obstructive hydrocephalus) G91.2 (normal-pressure hydrocephalus) G94 (hydrocephalus, other) G91.8 (other hydrocephalus) G91.9 (hydrocephalus, unspecified)
Diabetic metabolic encephalopathy	E15 (non-diabetic hypoglycaemic coma) E16.1-E61.2 (other hypoglycaemia and hypoglycaemia, unspecified) E10.0 (insulin-dependent diabetes mellitus with coma) E10.4 (insulin-dependent diabetes mellitus with neurological complications) E11 (non-insulin dependent diabetes mellitus with coma) E11.4 (non-insulin dependent diabetes mellitus with neurological complications) E12 (malnutrition-related diabetes mellitus with neurological

	complications)
	E13 (other specified diabetes mellitus with coma)
	E14.0 (unspecified diabetes mellitus with coma)
	E14.4 (unspecified diabetes mellitus with coma)
Other encephalopathies	B15 (hepatitis A with hepatic coma)
	B16 (hepatitis B with hepatic coma [with delta agent])
	B16.2 (hepatitis B with hepatic coma [without delta agent])
	B19 (unspecified viral hepatitis with hepatic coma)
	E03.5 (myxoedema coma)
	E51.2 (Wernicke's encephalopathy)
	G93.4 (encephalopathy, unspecified and metabolic)
	G93.5 (non-traumatic compression of brain)
	G93.6 (non-traumatic cerebral oedema)
	I67.4 (hypertensive encephalopathy)
	T67 (heat stroke)

1.1.2 Disease burden NTBPs

There is a paucity of research on the prevalence or incidence, morbidity and mortality of NTBP.[9] One study conducted in the province of Ontario, Canada found that persons with traumatic brain pathologies were younger, male and more likely to live in rural areas compared to non-TBIs.[13] NTBP patients also had more comorbidities and more mental health diagnoses.[13] Among older adults aged 65 years or more, NTBPs covered brain tumours (44%), anoxia injury (20%) and vascular insults (14%),[13] and had elevated costs for health care compared to TBI. Notably, a separate Ontario-based study found that annual NTBP medical costs totalled CAD$368.7 million versus CAD$120.7 million for brain injury.[14]

Although a disease burden among the elderly, children can be affected, with at least 10% of NTBP cases reported in patients under the age of 18.[15] Such pathologies are often overlooked as a source of long-lasting sequelae and subsequent expenditure to the healthcare system.[16] Contrary to adults, children present with a different distribution of NTBP: across the types of diagnoses, toxic effect of substance episodes of care was found to be the highest (22.7 per 100,000 persons annually), followed by brain tumour episodes of care (18.4 per 100,000 persons annually) and meningitis (15.4 per 100,000 persons annually).[15]

In Australia, acquired brain injuries are a substantial disease problem, with incidence ranging from 57 to 377 per 100,000 persons, compared to an estimated range of 100 to 270 per 100,000 annually overseas.[8] However, domestic data on prevalence and incidence of NTBPs in Australia are less easily identified than for brain trauma.[8] Even so, some statistics on NTBP conditions are available nationally. The Australian National Hospital Morbidity Database indicates that stroke accounts for an incidence of 280 per 100,000 persons, anoxic brain injury precipitates 19 per 100,000 and alcohol-related brain injury stands at 15 per 100,000 persons each year.[8]

1.1.3 Coma and airway compromise in NTBPs

NTBP causes dysfunction of the neurons, which can lead to injury and death. Coma is a common presentation, with 40% of patients presenting to emergency with persistent coma (≥ 6 hours) due to ingestion of alcohol and other toxic substances, and 25% due to hypoxic/anoxic injury after cardiac arrest.[17] Coma, which can be caused by NTBP, results

from dysfunction of the brain's ascending reticular activating system (ARAS), which is responsible for arousal and conservation of alertness.[17,18] In this sense, coma is a state of *un*arousable unconsciousness caused by an insult to the ARAS.[17] It is perhaps self-evident that for NTBP to produce coma, the ARAS must be functionally interrupted, diffusely or at important activation sites.[17]

Such pathological disruption can produce either transient or even permanent coma. Structural brain lesions such as those caused by ischaemic stroke, haemorrhagic stroke, inflammatory lesions or tumours can compress or destroy brain parenchyma,[17-19] while lesions that involve the rostral ARAS, diencephalons and cerebral cortex can and do produce acute coma.[17] Supratentorial mass lesions caused by strokes or tumours can also cause coma by producing 'herniation', shifting brain structures from one intracranial compartment into another. Meanwhile, the diencephalon can herniate through the tentorial opening, affecting ARAS and (thus) producing coma.[20]

NTBPs can also be caused by metabolic, nutritional and toxic encephalopathies.[3] Examples of pathologies that cause many of these diseases include organ failure (liver, renal, lung, cardiovascular or adrenal), electrolyte disturbances (hypo and hypernatraemia, derangements of calcium, and hypo or hypermagnesaemia), hypo and hyperglycaemia, disturbances in thyroid function or inborn derangements of metabolism.[17] These encephalopathies that result from imbalances in electrolytes, organ failure or metabolic derangements typically cause a brain-diffuse, reversible encephalopathy without any localising signs. It is likely that these disorders cause additional alteration of the polysynaptic function in the ARAS.[17]

Infections can likewise cause inflammation that results in NTBP (including encephalopathies) and present similar to diseases caused by metabolic derangements.[21] Mechanisms that could cause ARAS disruption by the inflammatory effects of systemic or brain infections include impairment of microcirculation, alterations of neurotransmitters, the effect of cytokines and free radicals.[21] Concurrently, inflammatory processes operating in brain infections alter the blood–brain barrier permeability, resulting in vasogenic cerebral oedema with leakage of serum proteins and other molecules into the cerebrospinal fluid. These purulent exudative processes could ultimately result in the blockage of cerebrospinal

fluid flow, causing hydrocephalus and interstitial oedema.[17] Exudate narrows the diameter of the large arteries of the brain base, with inflammatory cells infiltrating the arterial wall causing alterations in cerebral blood flow, which result in cerebral ischaemia and subsequent neurological deficits and stroke.[17] Thus, it follows that purulent meningitis leads to brain oedema, hydrocephalus, seizure, and ischaemic and haemorrhagic infarcts.

Practically, a comatose NTBP patient might present to the emergency physician, nurse or paramedic as mere failure to open one's eyes or respond to stimulation, or with simple withdrawal-type movements and a verbal response no better than simple vocalisation of non-word noises.[17] The depth of coma is typically measured in the emergency setting by the Glasgow Coma Scale (GCS),[22,23] where lower GCS corresponds with deeper coma.[17,18] Coma due to NTBP is a medical emergency, as it can result in secondary brain damage caused by brain haemorrhage, raised intracranial pressure, seizure and loss of airway control.[17] Airway management in comatose patients is thought to be essential to prevent aspiration of stomach contents and asphyxia due to airway collapse.[17] Endotracheal intubation using techniques such as RSI is the mainstay of airway management.[24]

1.1.4 What is RSI?

Endotracheal intubation is the process in which a tube is inserted into the trachea to oxygenate, ventilate and protect critically ill patients from aspiration.[25] Endotracheal intubation is utilised in patients that are considered at high risk of inhaling stomach contents, such as those that are comatose due to NTBP,[17] thus, risking exposure to increased risk of pneumonia.[26-28] Aspiration is not uncommon in emergency settings, with 1:600–900 cases reported—which is far more frequent than elective procedures (1:3,000–4,000).[29-31] Indeed, pulmonary aspiration has long been recognised as a cause of death during anaesthesia. In 1950, the Association of Anaesthetists of Great Britain and Ireland found that 43 deaths were caused by regurgitation and aspiration, and by 1956 a further 110 deaths were attributed to aspiration of gastric contents.[32] The consequences of pulmonary aspiration are dire, with acidic solids and liquids breathed into the lungs known to induce severe aspiration pneumonitis in many, resulting in lobar pneumonia with cyanosis, tachycardia, dyspnoea, mediastinal shift, consolidation and greater morbidity.[33] Endotracheal intubation aims to avoid pulmonary aspiration by sealing the trachea with a cuffed plastic tube; this physically blocks

the stomach contents from entering the lungs.[28] Gastric insufflation of the stomach is also avoided if all ventilation is given though the endotracheal tube.[34]

Intubation of the trachea can proceed using a variety of methods, ranging from 'cold' intubation, which proceeds without the use of any drugs, to drug-assisted intubation, where the patient receives medication before and after insertion of the endotracheal tube. Rapid sequence intubation (RSI) is one such drug-assisted endotracheal technique in which patients receive anaesthesia before intubation. First, the lungs are pre-filled with oxygen before administering rapid-onset sedative or hypnotic and neuromuscular-blocking drugs that cause coma and paralysis; after, a plastic endotracheal tube is inserted to secure the airway.[35] Typically, RSI utilises a muscle-blocking agent that relaxes all musculature and causes the patient to stop breathing.[3] Classically, RSI employed thiopental and succinylcholine, but in later years etomidate and (even later) propofol were used alongside muscle-relaxant agents.[33] Recent variations of RSI utilise non-depolarising neuromuscular-blocking agents and opioids. Additional drugs such as atropine, lidocaine, ketamine as well as benzodiazepines such as midazolam are used to facilitate RSI, as is administered by paramedics in Victoria, Australia.[36]

RSI is used by physicians in emergency departments and increasingly by paramedics in out-of-hospital settings.[37,38] Although the extent of its practice by emergency medical services (EMS) globally is not known, numerous out-of-hospital agencies in Australia, Europe, South Africa and the United States utilise RSI.[39-43] Practically, the procedure facilitates a variety of pathologies such as acquired brain injury, along with brain trauma and NTBP. As an example, Mobile Intensive Care Ambulance (MICA) paramedics in Victoria are authorised to provide RSI to patients that have a GCS of less than 10 due to head trauma, NTBP, respiratory failure, severe hyperthermia, severe uncontrolled pain and airway burns.[36] That said, paramedic use of RSI is not without controversy, with concerns raised regarding its success and adverse event rates being poorer than those of emergency physicians.[24,38] A recent systematic review also showed that RSI by paramedics have poorer first pass and overall success proportions, as well as higher adverse event rates such as hypoxia, endobronchial intubation and hyperventilation.[38] However, this review found that some EMS jurisdictions use RSI with proficiency that is on par with out-of-hospital emergency physicians and anaesthesiologists.

Some paramedic RSI systems, such as those in Victoria, exceed the pooled success and adverse event rates found in this reveiw,[44] showing that with adequate training, paramedics can administer RSI proficiently. Evidently, then, RSI is a complicated and potentially risky procedure, so its application for conditions such as NTBP needs a solid evidence base.

1.1.5 Lack of high-quality evidence to support paramedic RSI

Generally, little evidence supports the use of RSI for NTBP in emergency settings, whether employed in departments or by services.[35] However, some RSI literature exists in relation to brain injury. Notably, in 2003 Davis et al. published the results of an historically-controlled trial of RSI by paramedics for TBI,[45] which saw 209 recipients of intubation using midazolam and succinylcholine prospectively enrolled and compared to an historical cohort of 627 patients. The RSI group had significantly worse survival compared to controls (33.0% v. 24.2%, $p < 0.05$), with incidence of a 'good outcome' lower in the former compared to the latter (45.5% v. 57.9%, $p < 0.01$).[45] A subgroup analysis of the Davis et al. trial suggested that the poorer results could be attributable to inappropriate ventilation and hypoxemia.[45]

Of course, these results are perhaps biased by the limitations inherent in historically controlled trials. It is unclear that the RSI and historical controls were similar in confounding factors, as such data can result in selection bias, decreased power and increased type I errors.[46] Thus, a more recent Australian randomised controlled trial (RCT) on TBI by Bernard et al. avoided the pitfalls of the Davis example. In comparing paramedic RSI to emergency department intubation,[39] the median-extended Glasgow Outcome Score at six months was 5 in patients that received RSI by paramedics compared with 3 in those intubated at hospital ($P = 0.28$). Even though the main outcome showed no significant difference, a secondary outcome was meaningfully different: the proportion with a favourable outcome (Glasgow Outcome Score, 5–8) was 51% in the paramedic RSI group compared with 39% in the hospital intubation group (risk ratio 1.28; 95% confidence interval [CI] 1.00–1.64; $P = 0.046$).[39] Importantly, Bernard et al. found a 3% non-significant survival-to-hospital discharge advantage for paramedic RSI.

With over 230 citations,[47] the Bernard et al. trial is a landmark study and the only RCT to guide RSI for any indication, either prehospitally or in an emergency department. Although it

is used internationally to support the practice of RSI by paramedics, the trial has received criticism for its apparent shortcomings, suggesting that it might be unsuitable to justify RSI by paramedics. Fitzgerald et al. stated that no correction was made for the multiple secondary outcomes, deeming those used to justify paramedic RSI subsequently responsible for increasing the outcome data by chance.[47] It is also apparent that the Bernard trial might have been too small in terms of sample size, and that the significant secondary outcome found could be a chance finding. The implication of these criticisms implies that this RCT might not serve as an adequate evidence basis for paramedic RSI. Evidently, there is clinical equipoise for evidence on paramedic RSI, with a trial urgently needed.[48]

Even if the Bernard trial did not have the shortcomings suggested by Fitzgerald et al., it remains unclear that evidence from a brain trauma study can be applied to examine NTBP, as such patients are comparatively different in several ways.[7] For example, consider that mechanical ventilation increases intrathoracic pressures[49] and RSI patients receive such ventilation. Since myocardial dysfunction is often found in subarachnoid haemorrhage (and perhaps other strokes),[50] and given that positive pressure ventilation can decrease cardiac output, it follows that ventilation after RSI could decrease cardiac output in subarachnoid haemorrhage.[49] If plausible, perhaps intubation could do so for other types of stroke and NTBPs. Conversely, a recent prospective study shows that TBI is not linked with myocardial dysfunction in contrast to subarachnoid haemorrhage.[50] It stands to reason that positive pressure ventilation after RSI could affect mortality differently when brain trauma and NTBPs are compared.

While it is possible that RSI-related mechanical ventilation could affect survival differently for brain trauma patients compared to NTBPs, other potential mechanisms could inhibit application of the trauma evidence to NTBPs. Primarily, patients intubated for TBI are younger than those with stroke.[42] As age is associated with increased mortality from nosocomial infections following mechanical ventilation,[51] and given that many patients with NTBPs such as strokes are older than those with TBI, intubation could actually cause more infection in stroke compared to brain trauma. Similarly, increased age is associated with increased risk of RSI-related hypotension.[52] Since stroke patients tend to be older than TBI, it follows that the elderly stroke patient might be more prone to low blood pressure compared to

individuals with brain trauma. Undoubtedly, there are other factors that separate NTBP patients from their TBI counterparts. Thus, it is argued that mechanical ventilation and the age effects on nosocomial infections and hypotension together suggest that the evidence from the Bernard RSI trial in brain trauma cannot necessarily be applied to NTBPs.[39]

1.2 Rationale for the research in this thesis

As indicated in Section 1.1, NTBPs such as stroke, seizure and encephalopathies caused by toxidromes comprise a substantial proportion of acquired brain injuries (at least, from what can be gleaned from the sparse research on this topic). It is also apparent that NTBPs are a cause of coma and (therefore) a common cause of presentations to both emergency departments and the EMS. If NTBPs were common in those that receive RSI, and, conversely, if RSI were prevalent in NTBP, then it is clear that high-quality evidence to support intubation for NTBPs is needed.

A cursory literature search showed a shortage of studies outlining the exact prevalence of NTBPs in RSI recipients, with the inverse remaining equally true: there are few, if any, studies that report the true proportion of RSI in patients with NTBPs. Again, this is important knowledge, as the greater the amount of patients contributing to increased disease burden, the more pressing the need for quality evidence to support RSI in out-of-hospital settings. While a quick literature review revealed few studies that aim to answer these questions, it was clear that at least *some* research does provide a modicum of the prevalence of NTBPs receiving RSI.

Bernard et al. conducted a study counting the prevalence of non-traumatic coma in a group of patients that received RSI over a four-year period in Victoria.[53] The authors found that 551 of 1,152 (48%) RSIs were conducted on individuals that paramedics considered to have experienced non-traumatic coma. However, they could not stratify this incidence into the various pathologies that comprise NTBPs, as paramedics were limited in their diagnostic capabilities prehospitally. Wholly dependent on paramedic provisional diagnosis and further restricted by their inability to (for example) diagnose stroke (as no radiological capabilities exist in ambulances), the Bernard et al. study suffers key limitations. Seemingly the only work to date to compute the prevalence of NTBPs in RSI recipients, this research falls short of

providing a true prevalence for non-traumatic coma. To get an accurate picture of NTBP incidence in paramedic RSI cohorts, it is critical to count hospital-based diagnosis, since this is more likely to be correct and less biased. Overall, these estimates will provide a truer indication of the NTBP burden in patients that receive RSI by paramedics, and further serve to inform the importance of a solid intubation evidence base.

There is merit in knowing the true prevalence of NTBPs in RSI administered by paramedics, but current research is not adequate for this purpose. To do so, Eqn. 1 denotes the prevalence of NTBP in RSI:

$$\text{Prevalence of non} - \text{traumatic brain pathologies in RSI} = \frac{Number\ of\ NTBP}{Number\ of\ RSI} \qquad (1)$$

It is equally critical to grasp the inverse. Hence, Eqn. 2 denotes the prevalence of RSI in NTBPs:

$$\text{Prevalence of RSI in non} - \text{traumatic brain pathologies} = \frac{Number\ of\ RSI}{Number\ of\ NTBP} \qquad (2)$$

Reckoning both prevalence estimates, in which the numerator and denominator are exchanged, will highlight the true burden of NTBPs. Knowing both these prevalence estimates, where the numerator and denominator are switched around, will give us an idea of the true burden of non-traumatic brain pathologies, and an inference for the urgency of quality evidence to support RSI would be easier as a consequence. There are no high quality trials to support the use of RSI in non-traumatic brain pathologies. The brain trauma patient might differ too much from the non-traumatic brain pathology patient, and the evidence is not transferable.

1.3 Aims and objectives of this thesis

This thesis, and the research that informs it, aims to calculate the prevalence of RSI in NTBPs (and vice versa), further employing observational methods to examine whether intubation benefits such pathology. Furthermore, this thesis aims to determine whether brain trauma evidence can reasonably inform NTBP RSI. In sum, the research objectives include:

1. quantifying the prevalence of RSI by paramedics in NTBPs presented in out-of-hospital settings

2. further enumerating the proportion of NTBPs in patients receiving RSI (Note that this is the inverse of the prevalence that is calculated in the previous point)
3. measuring the survival benefit (or harm) of paramedic RSI in the most common NTBPs revealed by the first two studies—which the researcher a priori hypothesised as either stroke or seizure
4. investigating if RSI affects survival similarly for TBI versus non-TBI to determine whether researchers can use brain trauma evidence to guide non-trauma intubation
5. guiding methodologies to further research the effectiveness of RSI for NTBPs that are more rigorous than the observational methods employed in this study.

1.4 Chapters of this thesis

This thesis is broadly outlined in seven chapters. The first introduces the research, and the second provides a systematic review quantifying the prevalence of RSI in NTBPs in emergency settings (i.e., emergency departments and out-of-hospital settings). This review will also enumerate survival proportions associated with RSI for various pathologies.

Next, Chapters 3 and 4 include observational studies. The former counts the prevalence of NTBPs in a cohort of paramedic RSI, and the latter is based on a large-linked dataset that uses propensity score matching to evaluate the survival benefit of RSI in a cohort of strokes.

Similar to Chapter 4, Chapter 5 and 6 are also observational studies based on a large linked dataset that aimed to find the mechanisms underlying different survival for RSI versus none. Also, statistical interactions explore the mechanisms that underpin differential survival of RSI when comparing brain trauma to strokes. This reveals whether the controlled trial evidence from brain trauma RSI can be applied to strokes. All observational studies in this thesis received ethics approval from the Monash University, and the certificates are shown in appendix A and B. Finally, this thesis closes with the key findings, implications and recommendations of the research in Chapter 7, including a formal conclusion.

Chapter 2: The prevalence of intubation in NTBPs

2.1 Declaration for Chapter 2

2.1.1 Monash University

Fouche PF, Stein C, Jennings PA, Smith K, Boyle M, Bernard S. Emergency endotracheal intubation in non-traumatic brain pathologies: a systematic review and meta-analysis. *Emerg Med Australas* [Internet] 2019; **31**(4): 533–41. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/1742-6723.13304 doi: 10.1111/1742-6723.13304

2.1.2 Declaration by candidate

In the case of Chapter 2, the nature and extent of my contribution to the work were the following:

Nature of contribution	Extent of contribution (%)
Lead author responsible for data collection, literature review, statistical analysis and manuscript preparation. Responsible author who accepts overall responsibility for publication.	85%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated.

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Paul Jennings	Manuscript preparation	–
Chris Stein	Quality ratings, manuscript preparation	–
Malcolm Boyle	Manuscript preparation	–
Karen Smith	Manuscript preparation	–
Stephen Bernard	Manuscript preparation	–

2.2 Background and context

Emergency intubation such as RSI is used to manage the airways of comatose patients with NTBPs including brain tumours, meningitis, encephalitis, anoxic injury, stroke, seizures, toxidromes, diabetic and other metabolic encephalopathies.[9,11,12] High quality evidence that justify RSI in NTBP is essential, but there is an apparent shortage of trials of advanced airway management for NTBP. However, RCT evidence exists to support RSI in TBIs, but it is unclear that this information can be extrapolated to NTBPs. Differences between TBI and NTBP patients are apparent, particularly regarding the effect of mechanical ventilation that follows intubation in RSI. Indeed, ventilation could worsen the low cardiac output states found in some strokes (which are comparatively less prevalent in brain trauma).[3,49] Another difference in comparing TBI and NTBPs regards the age-related propensity for nosocomial infections after intubation and ventilation. Generally, NTBPs such as strokes mostly occur in older cohorts than typical brain trauma.[3,42] Differences in the age distributions between TBI and NTBP could drive survival dissimilarities between both pathology types, since the likelihood of infection after intubation naturally increases with age. For these reasons the TBI evidence cannot be used to inform NTBP RSI, and finding studies that underpins RSI in NTBP is critical.

2.3 Aims of this chapter

Evidently, if the typical stroke patient differs from sufferers of TBI, and both pathologies might vary in response to intubation, then this suggests that the brain trauma evidence cannot be applied to stroke or seizure RSI. It would be equally important to find evidence that supports NTBP RSI by paramedics. The value of a rigorous research base would prove further critical if RSI were commonly used in pathologies such as brain tumours, meningitis, encephalitis, anoxic injury, stroke, seizures and toxidromes.

The systematic review and meta-analysis in this chapter aimed to discover and collate evidence that supports RSI in NTBPs in both emergency departments and out-of-hospital settings. Additionally, determining the extent of RSI use in these pathologies by calculating the prevalence of intubation for various NTBPs is equally important. To gauge the prevalence and uncover the evidence base upon which to support RSI in these pathologies, both a

systematic review and meta-analysis of all intubation (not just RSI) were performed. Included in the meta-analysis are paramedic-based studies and those from emergency departments in order to compare estimates from these two settings. This analysis employs a new method of pooling study-level statistics. The quality effects model enables adjustment for study-level bias, which could produce pooled estimates that are truer.[54] Additionally, and to enable proper quality ratings of all included studies, both a custom quality checklist and accompanying guide were developed to reduce inter-rater variation. The list was modified from the Hoy et al. prevalence checklist[55] and refined over three years, after which it was utilised (along with the guide) in two other advanced airway systematic reviews.[37,38] One key strength of this review is the large number of studies included, as well as use of a novel statistical method and bias adjustment to produce truer estimates.

EMA Emergency Medicine Australasia

Emergency Medicine Australasia (2019) doi: 10.1111/1742-6723.13304

REVIEW ARTICLE

Review article: Emergency endotracheal intubation in non-traumatic brain pathologies: A systematic review and meta-analysis

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Abstract

Endotracheal intubation is an advanced airway procedure performed in the ED and the out-of-hospital setting for acquired brain injuries that include non-traumatic brain pathologies such as stroke, encephalopathies, seizures and toxidromes. Controlled trial evidence supports intubation in traumatic brain injuries, but it is not clear that this evidence can be applied to non-traumatic brain pathologies. We sought to analyse the impact of emergency intubation on survival in non-traumatic brain pathologies and also to quantify the prevalence of intubation in these pathologies. We conducted a systematic literature search of Medline, Embase and the Cochrane Library. Eligibility, data extraction and assessment of risk of bias were assessed independently by two reviewers. A bias-adjusted meta-analysis using a quality-effects model pooled prevalence of intubation in non-traumatic brain pathologies. Forty-six studies were included in this systematic review. No studies were suitable for meta-analysis the primary outcome of survival. Thirty-nine studies reported the prevalence of intubation in non-traumatic brain pathologies and a meta-analysis showed that emergency intubation was used in 12% (95% CI 0–33) of pathologies. Endotracheal intubation was used commonly in haemorrhagic stroke 79% (95% CI 47–100) and to a lesser extent for seizures 18% (95% CI 10–27) and toxidromes 25% (95% CI 6–48). This systematic review shows that there is no high-quality clinical evidence to support or refute emergency intubation in non-traumatic brain pathologies. Our analysis shows that intubation is commonly used in non-traumatic brain pathologies, and the need for rigorous evidence is apparent.

Key words: *emergency, endotracheal intubation, non-traumatic brain pathologies.*

Key findings

- This meta-analysis shows that endotracheal intubation is commonly used in the ED and out-of-hospital setting.
- However, this study found no reliable evidence that supports or refutes the use of emergency endotracheal intubation for non-traumatic brain pathologies in the emergency setting
- A trial is urgently needed.

Introduction

Endotracheal intubation (ETI) is performed in the emergency setting for acquired brain injuries that include traumatic brain injury and non-traumatic brain pathologies. Non-traumatic brain pathologies comprise brain tumours, meningitis, encephalitis, anoxic injury, stroke, seizures, toxidromes, diabetic and other metabolic encephalopathies.[1–3] Controlled trial evidence for intubation in traumatic brain injury exists,[4] but it is not clear that this research can be applied to non-traumatic brain pathologies. Bernard *et al.* conducted a randomised controlled trial for out-of-hospital rapid sequence intubation (RSI) in head injury and found favourable neurological out- come at 6 months for paramedic RSI.[4] However, uncertainty exists if the Bernard *et al.* trial can be generalised to non-traumatic brain pathologies because of differences between traumatic brain injury and non-traumatic injuries to the brain.[5]

One such difference between traumatic brain injury and non-traumatic brain pathologies is the potential impact of mechanical ventilation. Mechanical ventilation follows intubation and could decrease cardiac output.[6] Patients with some

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Accepted 5 April 2019

types of non-traumatic brain pathologies such as subarachnoid haemorrhage often have decreased cardiac output, in contrast to brain trauma.[7] It follows that mechanical ventilation after intubation could impact survival differently when traumatic brain injury is compared to some non-traumatic brain pathologies due to this difference in cardiac output.[5] Furthermore, those intubated for traumatic brain injury tend to be younger than those with stroke,[5,8] and since age is associated with increased mortality from nosocomial infections following mechanical ventilation,[9] and given that some non-traumatic brain pathologies such as strokes tend to be older than traumatic brain injury patients, intubation could cause more infections in stroke compared to brain trauma. These differing mechanisms of intubation in non-traumatic brain pathologies *versus* traumatic brain injury suggest that extrapolating the traumatic brain injury evidence to non-traumatic brain pathologies might not be reasonable.

This study aims to review the available research that compares non-traumatic brain pathologies survival for those that receive emergency intubation to patients who do not. Additionally, if non-traumatic brain pathology intubation is commonly used in the emergency setting then the value of quality evidence becomes more important. To that end we aim to quantify the prevalence of emergency intubation in non-traumatic brain pathologies.

Methods

We conducted this systematic review using the PRISMA guidelines,[10] and this review was registered with the PROSPERO register (registration number CRD42016037970).

Data sources, search strategy and study selection

Two authors (CS and PFF) searched Medline, EMBASE, and the Cochrane Central Register of Controlled Trials from the inception of these databases up to 30 October 2017 (search terms in Appendix S1). The same authors also screened abstracts and full text of potentially suitable articles for applicability.

Eligibility criteria

Eligible studies included all out-of-hospital and in-hospital observational and experimental studies that report emergency intubation survival and/or intubation proportions in non-traumatic brain pathologies. Emergency intubation does take place in hospital settings outside of the ED; however, we limited our inclusion to intubation conducted in the ED or out-of-hospital setting only. The time frame for the selected studies was without limits. Publication types from which studies were sourced were limited to journal articles. Excluded were studies that report results from which it was impossible to extract survival statistics or prevalence proportions and those that report statistics for supraglottic airways and other advanced airway interventions that are not ETI. Furthermore, we excluded studies on manikins and simulations, animals, abstract only research or research where it is impossible to assess methodological quality. Lastly we excluded studies where intubation was done in a non-emergency setting such as elective intubation in wards or surgical theatres or where it was impossible to ascertain if the intubation was emergent.

Data abstraction

Two authors conducted an independent review of each included study (CS and PFF). The following characteristics were identified and extracted: study and year of publication; location where intubation performed; practitioner performing ETI; type of non-traumatic brain pathology, cohort size and number of intubation as well survival proportions. Extraction was piloted on five studies. We resolved incongruities in extracted data by arbitration and consensus.

Bias assessment

Two different quality assessments were completed on included studies. For the primary outcome of survival between intubation and no-ETI, we used the Newcastle–Ottawa scale.[11] The Newcastle–Ottawa scale is designed to assess the extent of bias of nonrandomised studies in meta-analyses by assessing the selection of study participants, comparability of exposed and unexposed cohorts and ascertainment of outcomes. A good rating needed three or four stars in selection, one or two stars in comparability, and two or three stars for the outcomes sections. A fair rating required two stars in selection, one or two stars in comparability, and two or three stars in outcomes. A poor quality rating reflected zero or one star in selection, or zero stars in comparability, or zero or one star in outcomes.

We quantified the bias of each study for the intubation prevalence of non-traumatic brain pathologies using a validated prevalence checklist by Hoy *et al*. (Appendix S2).[12] Hoy *et al*. recommended adapting their checklist for the specific needs of a study, and we did so by paraphrasing or modifying each item of the Hoy checklist. The checklist comprised of eight items that assessed external and internal validity by evaluating selection and non-response bias, measurement bias and bias related to analysis.[12] Modifications of the Hoy checklist included altering item one to assess generalisability with a focus on case mix since the proportion of very sick patients could conceivably alter the intubation prevalence. A modification of items five and six focused on the adequacy of non-traumatic brain pathology definitions and reliability of intubation success verification. Additionally, we designed a guide that accompanied the checklist to aid assessment (Appendix S3).

Two authors (CS and PFF) independently evaluated all included studies for bias related to the both the prevalence of intubation and survival using the Hoy checklist and the Newcastle–Ottawa scale. Inter-rater agreement was calculated using a weighted Cohens Kappa.[13] To adjust for study level bias using the QE model for the prevalence meta-analysis, we averaged the integer bias scores of each rater (out of

TABLE 1. *Meta-analytic results of intubation prevalence in non-traumatic brain pathologies, quality effects model*

	Prevalence bias score (category)	No. studies	Intubation proportion (%)	LCI 95%	HCI 95%	I^2 (%)	Cochran's Q
Subgroup							
All non-traumatic brain pathologies subgroups	4.3 (moderate)	39	12.0	0.0	33.0	99	3610
Seizures	4.2 (moderate)	21	18.0	10.0	27.0	97	691
Haemorrhagic stroke	4.5 (moderate)	2	79.0	47.0	100.0	83	5.91
Ischaemic stroke	5.0 (moderate)	3	6.0	0.0	32.0	99	346
Mixed stroke	5.0 (moderate)	1	31.0	20.0	43.0	NA	NA
Toxidromes	4.4 (moderate)	10	25.0	6.0	48.0	95	180
Encephalopathy	3.5 (high)	1	67.0	51.0	81.0	NA	NA
Mixed non-traumatic brain pathologies	3.0 (high)	1	26.0	16.0	37.0	NA	NA

HCI, higher confidence interval; LCI, lower confidence interval; NA, not applicable, too few studies for pooling.

the eight items listed in our bias checklist) (Table 1). The final Newcastle–Ottawa scale was reached on consensus between the two raters. Rating was piloted on five studies.

Definitions

Non-traumatic brain pathologies are defined as injuries to the brain (either permanent or transient) from non-traumatic causes including brain tumours, meningitis, encephalitis, hypoxic/anoxic brain injury, stroke, arteriovenous malformation in brain vasculature, cancer, aneurysms, brain haemorrhage, as well as brain injury because of diabetes, seizures (including but not limited to status epilepticus) and toxicity, metabolic derangements, alcohol and drug injury.[1,2] We defined intubation success as an endotracheal tube seated beyond the vocal cords and placed optimally in the trachea, verified by another clinician or by technological means (e.g. end-tidal CO_2 monitoring). Even though emergency intubation is occasionally done in surgical settings, intensive care units and hospital wards, these are mostly locales for elective intubation. Conversely, elective intubation is sometimes done in the ED and prehospitally, but is much more likely that emergency intubation takes place in those settings. Therefore, we focused solely on intubation in EDs and in the out-of-hospital setting. To that end we define emergent intubation as intubation by an authorised clinician in an ED or the out-of-hospital setting.

Statistical analysis

The main outcome is the survival proportion between an intubation and no-intubation group in non-traumatic brain pathologies. Secondarily, the prevalence of intubation in non-traumatic brain pathologies is calculated as a proportion. Both survival and prevalence are expressed as a percentage. Pooling of prevalence estimates used a double arcsine square root transformation to circumvent confidence intervals falling outside the range of 0–1, to stabilise variance and to reduce the chance of placing excessive weight on studies with extreme proportions.[14] Pooled results were then back-transformed to natural proportions.[14] If I^2 was greater than 50% or if τ^2 was greater than zero then heterogeneity was consid- ered likely. Both I^2 and Cochran's Q are presented for comparison. This meta-analysis was completed using the quality effects (QE) model.[15,16] Average ratings from the Hoy prevalence checklist served as weights in the QE model. The QE model corrects for study-level risk of bias and has been used in previous advanced airways meta-analysis.[17–19]

We estimated the risk of publication bias by visually examining Doi plots and assessing the Luis Furuya-Kanamori (LFK) index, rather than funnel plots.[20–22] Funnel plots perform poorly when the effect size is a prevalence proportion.[23] The LFK index outperformed Egger's regression for detection of asymmetry because of biases caused by selective publication.[22] The Doi plot uses a folded variant of the normal quantile-*versus*-effect plot. A symmetrical triangle is created with a z-score close to zero at its top. Asymmetric Doi plots implies that small study effects (and related biases) may have affected the pooled effect estimate.[20] The LFK index indicates no asymmetry if within ± 1 unit, with values more extreme than ± 1 unit implying asymmetry, but only if the asymmetry is in the same direction as the *a priori* judgement of the direction of suspected bias.[21,22]

Results

The literature search yielded 2918 articles. After abstract screening and duplicate exclusion, 46 articles were included in the systematic review; however, none were suitable for

pooling of the primary outcome of survival. Thirty-nine studies were appropriate for meta-analysis of prevalence of intubation in non-traumatic brain pathologies (Fig. 1). The seven studies that were not suitable for prevalence-of-intubation pooling had cohorts that consisted entirely of those that were intubated, making a calculation of prevalence impossible.[5,24–29] A comprehensive listing of the 46 articles with a description of study characteristics, prevalence-bias assessment, and intubation prevalence are shown in Table S1.[5,24–68]

Characteristics of the studies

Eight studies were prospective, of which three were randomised controlled trials. Three were case series, and one a historically controlled trial. Thirty-four (74%) were retrospective studies. Thirty (65%) had intubations performed in the ED, and eight (17.5%) in the out-of-hospital setting. A further eight studies reported intubation performed in both ED and out-of-hospital settings. Twenty-four (52%) studies did not report the type of clinician performing the intubation and physicians intubated in 11 (24%), with paramedics intubating in four (9%) or physician/non-physician teams intubating in seven (15%).

Twenty-two (48%) studies were on seizures and 10 (22%) were toxidromes or toxic encephalopathies. Seven studies reported on stroke cohorts, of which two (4%) were haemorrhagic and three ischaemic strokes (7%) and two (4%) were mixed stroke aetiologies. Six (13%) studies were an assortment of non-traumatic brain pathologies and one study reported on mixed encephalopathies. Most studies (83%) did not describe the type of intubation used, but eight (17%) stated that RSI was the preferred method (Table S1).

Study-level bias assessment

Two raters had perfect agreement for the Newcastle–Ottawa scale with a Kappa of 1.0 and good agreement for items of the prevalence-bias checklist with a Kappa of 0.51 (95% CI 0.24–0.77). Five studies compared an intubation to no-intubation cohort. For these five studies, the Newcastle–Ottawa scale reveal substantial bias since none properly accounted for important confounding variables such as illness severity or comorbidity, which limited comparability (Table S3).

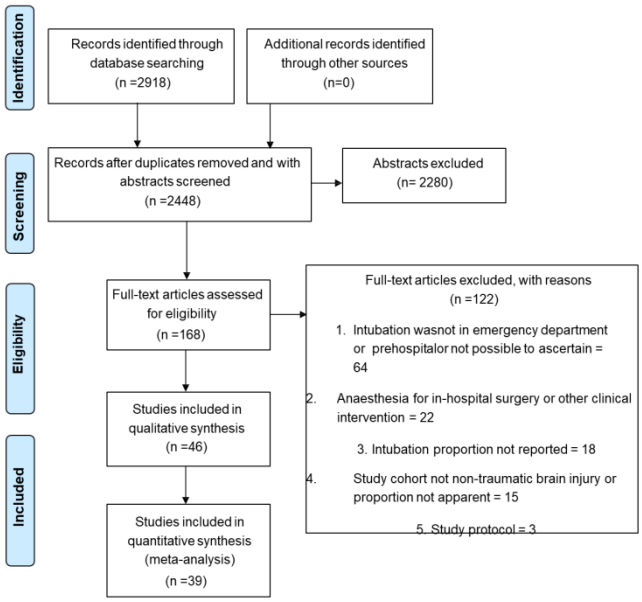

Figure 1. *Study selection flowchart.*

Quantitative synthesis

Non-traumatic brain pathology intubation survival

Ten studies reported non-traumatic brain pathologies survival of at least an intubation cohort, but none were suitable for meta-analysis since there were not enough of the various non-traumatic brain pathologies subgroups, or the subgroups were too variable within themselves to permit pooling.

Studies with comparison groups

Five of the 10 studies that report survival had a non-intubation comparison group. Three studies reported on toxicity or toxic encephalopathies, with 88% intubation survival for a ED study by Katz *et al*. (cannabinoid intoxication),[40] a 100% survival for ED based Kohli *et al*. (paediatric poisoning) and 100% for ED and out-of-hospital intubation by Perry *et al*. (baclofen overdose).[41,51] All three studies had complete survival in their non-intubation group. Only one study reported survival after intuba- tion for seizures: an intubation study by Vohra *et al*. set in both ED and out-of-hospital showed that 93% of the intubation group survived com- pared to 99% of those that did not receive ETI. Finally, in an ED study of encephalopathies, Vicario *et al*. reported a 69% intubation survival, compared to the non-intubation group that had 100% survival.[63]

Studies with no comparison groups

Theodosiou *et al*. showed that in an ED cohort consisting of haemorrhagic and ischaemic stroke 16% of intubation survived, but no

estimates for non-intubation were reported.[27] Two studies provide survival estimates for ischaemic stroke: Petchy *et al*.[52] showed their ED and out-of-hospital intubation cohort had 16% survival and Santoli *et al*. with 28% ED-based survival, also with no comparison groups.[55] A further two studies report survival outcomes for a heterogeneous group of non-traumatic brain pathologies: Fouche *et al*. demonstrated that their out-of-hospital RSI cohort had a 69% survival[5] and Pakkanen *et al*. showed a 65% intubation survival for the non-traumatic brain pathologies in their out-of-hospital study.[25]

Prevalence of emergency intubation in non-traumatic brain pathologies

The prevalence of intubation for the seizure subgroup is 18% (95% CI 10–27); haemorrhagic stroke is 79% (95% CI 47–100); ischaemic stroke is 6% (95% CI 0.0–32). For ischaemic strokes, a large study by Petchy *et al*. contributed disproportionally to the 6% intubation estimate. In a sensitivity analysis, the removal of Petchy *et al*. raised the prevalence of intubation in ischaemic strokes to 25% (95% CI 22–28).[52] The pooled estimate for intubation in toxidromes is 25% (95% CI 6.0–48).

Three studies reported the prevalence of RSI in their non-traumatic brain pathologies cohorts. Lewena *et al*. showed in two studies of seizures that out-of-hospital RSI was done in 48% (95% CI 7.0–91) when pooling these two studies.[44,45] Meyer *et al*. reported out-of-hospital RSI in haemorrhagic stroke, and found that 55% of their cohort received RSI.[47] The prevalence of intubation in all non-traumatic brain pathologies for EDs and the out-of-hospital setting pooled together is 12% (95% CI 0.0–33) (Tables 1,S2, Fig. 2). There was an insufficient number of out-of-hospital studies for the various non-traumatic brain pathologies suitable for meta-analysis to permit a comparison of intubation prevalence between the ED and out-of-hospital settings. However, Alldredge *et al*. showed that 42% of the out-of-hospital seizure cohort received ETI, compared to the pooled estimate of 18% for ED seizures (95% CI 10–27).[30] No comparison between physicians *versus* paramedic intubation prevalence was possible. The Doi plot for the overall intubation prevalence in non-traumatic brain pathologies was asymmetrical (LFK = 6.33 [major asymmetry]) (Fig. S1). All analyses showed large heterogeneity (Table 1).

Discussion

This systematic review shows that there is no high-quality evidence to support or refute the use of emergency ETI in non-traumatic brain pathologies. Twenty-two percent of included studies described survival for at least an intubation group, and five studies had a comparison group of no ETI. For studies that report survival for intubation compared to no-ETI, higher survival in the non-intubation groups is apparent. However, none of these studies were designed to show a causal link between intubation and survival in non-traumatic brain pathologies. To show a causal association between advanced airways and survival, it is important to ensure that the groups being compared have a similar baseline prognosis. To achieve such parity, an airway study must account for prognostic factors such as illness severity and comorbidities and perhaps the timing of intubation to avoid confounding by indication.[69,70] None of the studies that report survival adequately adjusts for these prognostic factors, as demonstrated by our Newcastle–Ottawa assessment. As such their results are unreliable and cannot inform practice. Even though the survival statistics reported here are likely biased, it is evident that survival varied by the type of non-traumatic brain pathologies. Our review shows that seizures and toxidromes had high survival. Conversely, strokes and encephalopathies had poor survival. These survival differences might be related to varying levels of illness severity between these pathologies, with haemorrhagic strokes having poorer prognosis compared to toxidromes and seizures. Some question the value of routinely intubating seizures and toxidromes in the emergency setting.[24]

There is a shortage of reliable research to support emergency intubation in non-traumatic brain pathologies. However, there is evidence of possible harm of intubation in non-traumatic brain pathologies such as stroke in a non-emergency setting. In large and well balanced retrospective studies of intubation for thrombectomy in stroke, poorer functional outcome and longer hospital stays for those that receive intubation is evident.[71,72] Similarly, a retrospective analysis of the IMS3 thrombectomy trial also showed

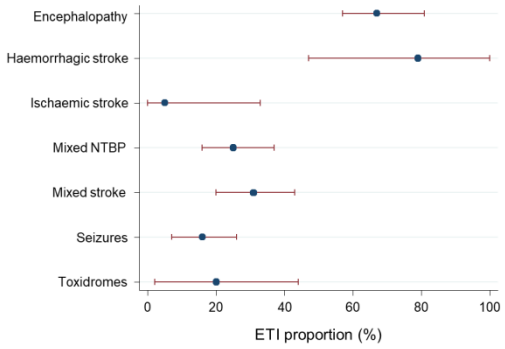

Figure 2. *Emergency intubation prevalence of non-traumatic brain pathology subgroups with 95% confidence intervals.*

increased risk of death in those intubated.[73] The conclusion that elective intubation might be detrimental carries more weight in these three studies since they were designed to compare intubation to no-intubation because these studies rigorously accounted for illness severity using stroke scales such as the NIHSS. Stated differently, the intubation *versus* no-intubation groups were more comparable for important prognostic factors, which is not the case for the studies included in our systematic review.

Takahashi *et al*. suggest that the decreased survival from intubation in stroke thrombectomy is likely caused by delays in procedure start times or that intubation and ventilation cause cerebral arterial vasoconstriction. Takahashi *et al*. also propose that cerebral perfusion pressures in stroke can be compromised due to hypotension caused by pre-intubation medications.[74]

Not only do prognostic factors such as illness severity impact survival, but mortality in non-traumatic brain pathologies intubation could also be impacted by the experience and training of the intubating clinician, as well as geographical variations in intubation competentcy.[5,18] Lack of relevant data in this review precluded investigation of these additional factors. To inform clinical practice, research should focus on emergency RSI, since it is likely to be the most widely used intubation technique in the ED.[75] Since most studies included here were ED based, it follows that most intubation could be RSI. RSI is also frequently used by out-of-hospital emergency services.[5,18,24]

The importance of a strong evidence base for non-traumatic brain pathologies emergency intubation increases if intubation is commonly used. Our meta-analysis shows that intubation is often utilised for non-traumatic brain pathologies in the ED and out-of-hospital settings, with 12% receiving intubation. This prevalence of intubation varies considerably depending on the type of non-traumatic brain pathologies. Haemorrhagic strokes have a high proportion of ETI, and likely reflects the large illness severity in this population. Conversely, seizures and also toxidromes have a much lower rate of ETI. Despite such a large variation in intubation prevalence between the various non-traumatic brain pathologies, it is clear that intubation is frequently used for these pathologies and the need for controlled trial evidence has become more pressing.

Conclusions

This systematic review shows that there is no high-quality evidence to support or refute emergency intubation in non-traumatic brain pathologies. Furthermore, our analysis shows that intubation is frequently used in non-traumatic brain pathologies. Since intubation in non-traumatic brain pathologies is common, the need for quality research in intubation for non-traumatic brain pathologies is important.

Limitations

This meta-analysis found large heterogeneity, similar to other advanced airway meta-analyses.[17,18,76] Heterogeneity in intubation prevalence is expected due to variations in intubation practices and also to varying levels of case-mix of included cohorts. We have accounted for these variations in illness severity by assessing and adjusting for case-mix using the QE model. Even with large heterogeneity, the central message is that intubation is widely used in emergency non-traumatic brain pathologies. Not only was heterogeneity apparent in the analysis, but the types of non-traumatic brain pathologies are much varied, and the pooling of the intubation prevalence for all the subgroups can at best be a crude description of how common intubation is used in non-traumatic brain pathologies. Also, it would be ideal to compare intubation prevalence and survival by ED *versus* out-of-hospital setting, but the studies included here did not permit such a comparison.

An inspection of the Doi plot, which shows gross positive asymmetry, suggests that there might be a shortage of smaller studies reporting lower proportions of ETI. We did not have any *a priori* reason to expect either under or over reporting of low or high prevalence, so the asymmetry is surprising. This might suggest that lower intubation proportions are underreported. We believe that it is unlikely that the addition of such studies will alter the conclusion that emergency intubation in NTB is extensively used.

Author contributions

PFF conceived of the study, CS and PFF completed the literature search, data extraction and bias ratings and PFF analysed all data. All contributed to the manuscript. PFF takes responsibility for the paper as a whole. The authors alone are responsible for the content and writing of the paper.

Competing interests

None declared.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Appendix S1. Search terms.
Appendix S2. Quality checklist for a systematic review of emergency intubation in non-traumatic brain pathologies.
Appendix S3. Guidelines for using the intubation in non-traumatic brain pathologies checklist.

*See Appendix C, Tables C.1.1 and figure C2.1 for the supplementary material

2.4 Principle findings and conclusions

The systematic review and meta-analysis show that endotracheal intubation and RSI are commonly used in both emergency departments and out-of-hospital settings, but no rigorous evidence actively supports emergency endotracheal intubation for NTBPs in either setting. Numerous observational studies that report survival are presented, but the quality assessment indicates that these are not unbiased enough to guide clinical practice. Importantly, the findings are based on all types of intubation, and not just RSI. That said, the review indicates that most intubations are likely RSI, and the conclusions gleaned are applicable to RSI itself. Since intubations (and RSI) are common for NTBPs, and given that no high-quality evidence supports RSI for these illnesses, it remains clear that a randomised trial is urgently needed.

Chapter 3: Survival in out-of-hospital RSI of NTBPs

3.1 Declaration for Chapter 3

3.1.1 Monash University

Fouche PF, Jennings PA, Smith K, et al. Survival in out-of-hospital rapid sequence intubation of non-traumatic brain pathologies. Prehosp Emerg Care [Internet] 2017; 21(6): 700–8. Available from: https://www.tandfonline.com/doi/abs/10.1080/10903127.2017.1325952?journalCode=ipec20 doi: 10.1080/10903127.2017.1325952

3.1.2 Declaration by candidate

In the case of Chapter 3, the nature and extent of my contribution to the work were the following:

Nature of contribution	Extent of contribution (%)
Lead author responsible for data collection, literature review, statistical analysis and manuscript preparation. Responsible author who accepts overall responsibility for publication.	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated.

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Paul Jennings	Manuscript preparation	–
Malcolm Boyle	Manuscript preparation	–
Karen Smith	Manuscript preparation, data collection	–
Stephen Bernard	Manuscript preparation	–
Gabriel Blecher	Manuscript preparation, data collection	–
Jonathan Knott	Manuscript preparation, data collection	–

Mani Raji	Manuscript preparation, data collection	–
Pamela Rosengarten	Manuscript preparation, data collection	–
Michael Augello	Manuscript preparation, data collection	–

3.2 Background and context

RSI is used to stabilise the airways of NTBPs in emergency settings. However, despite the procedure's clinical importance, no high-quality studies in the literature support its use for such pathologies.[2] Urgency to generate evidence that backs RSI for would be more pressing if the disease burden of NTBPs were sizable. That is, if many patients with strokes, seizures, encephalopathies and/or other non-TBIs were commonly intubated using RSI, then the urgency for clinical evidence becomes critical because more patient lives are at stake.

Through a systematic review, Chapter 2 showed that intubation methods such as RSI are common in NTBPs, both in emergency departments and in prehospital settings. Further, the meta-analysis found that emergency intubation was used in 12% of NTBPs, while endotracheal intubation was used commonly in haemorrhagic stroke (79%) and to a lesser extent for seizures (18%) and toxidromes (25%). Rapid sequence intubation proved to be the most common method of intubation in these studies.

It is clear that endotracheal intubation using RSI are commonly used in the ED and by paramedics. Even so, this systematic review did not tell us how prevalent non-traumatic brain pathologies are in RSI, which is the inverse of the prevalence of RSI in NTBP. To estimate this statistic the numerator and denominator needs to be inverted. Stated differently, instead of looking at the prevalence of RSI in non-traumatic brain pathologies, we also need to know the prevalence of these pathologies in RSI. The reason that this knowledge would be useful is that if stroke, seizures and so forth are common in RSI, then the training and evidence for nontrauma RSI would become important. It is possible to RSI a large proportion of NTBP (the finding of chapter two), but if NTBP are not prevalent, then the proportion of NTBP in RSI (the inverse) would become small. This counterintuitive situation emphasizes the need for a study that counts the prevalence of non-traumatic brain pathologies within a cohort of RSI.

3.3 Aims of this research

This cohort study was published in the *Prehospital Emergency Care* journal under the title 'Survival in out-of-hospital rapid sequence intubation of non-traumatic brain pathologies'. It aimed to calculate the prevalence of NTBPs in a sample of paramedic RSI in Victoria. Previous research has attempted to enumerate NTBP in RSI, but this was based on paramedic diagnosis, which is limited by the respective diagnostic capacities of EMS.[53] It is believed that using hospital-based ICD10-AM codes would result in less measurement bias and a more accurate NTBP prevalence estimate for intubation recipients.

Research governance approval was sought from seven Melbourne-based hospitals and Ambulance Victoria (AV), with data manually collected from in-hospital records by the principal investigators at each site. We anticipated that this study would take two years due to laborious data collection and recruiting principal investigators from each location. Such a multisite study would entail seeking governance approval from all participating Melbourne-based hospitals in addition to the manual data collection. Data had to be linked painstakingly due to differences in site-specific collection and storage practices.

In addition to calculating the prevalence of NTBPs in a cohort of RSI, the researchers aimed to uncover the out-of-hospital predictors of survival-to-hospital discharge. This information would be useful for future research and further serve as possible confounding variables that must be accounted for in statistical models.

Survival in Out-of-hospital Rapid Sequence Intubation of Non-Traumatic Brain Pathologies

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Abstract

Introduction: Rapid sequence intubation (RSI) is not only used in traumatic brain injuries in the out-of-hospital setting, but also for non-traumatic brain pathologies (NTBP) such as brain tumors, meningitis, encephalitis, hypoxic/anoxic brain injury, stroke, arteriovenous malformations, tumors, aneurysms, brain hemorrhage, as well as brain injury due to diabetes, seizures and toxicity, metabolic conditions, and alcohol and drug overdose. Previous research suggests that RSI is common in non-traumatic coma, but with an unknown prevalence of NTBP in those that receive RSI. If NTBP is common and if brain trauma RSI evidence is not valid for NTBP then a sizable proportion of NTBP receive this treatment without evidence of benefit. This study calculated the out-of-hospital NTBP prevalence in patients that had received RSI and explored factors that predicted survival. **Meth- ods:** A retrospective cohort study based on data collected from an ambulance service and seven hospitals based in Melbourne, Australia. Non-traumatic brain pathologies were defined using ICD10-AM codes for the calculation of NTBP prevalence. Logistic regression modelled out-of-hospital predictors of survival to hospital discharge after adjustment for comorbidities. **Results:** The seven participating hospi- tals treated 2,277 patients that received paramedic RSI for all illnesses and indications from January 1, 2008 to Decem- ber 31, 2015, with survival data available for 1,940 (85%). Of the 1,940, 1,125 (58%) patients had at least one hospital-diagnosed NTBP. Sixty-nine percent all of NTBP survived to hospital discharge, compared to 65% for traumatic intracranial injury. Strokes were the most common and had poor survival to discharge (37%) compared to the second most common NTBP toxicity/toxic encephalopathy that had very high survival (98%). No out-of-hospital clinical intervention or prehospital time interval predicted survival. Factors that did predict survival include Glasgow Coma Scale (GCS), duration of mechanical ventilation, age, ICU length of stay, and comorbidities. **Conclusions:** Non-traumatic brain pathologies are seven times more prevalent than traumatic brain injuries in patients that underwent out-of-hospital RSI in Victoria, Australia. Since the mechanisms through which RSI impacts mortality might differ between traumatic brain injuries and NTBP, and given that NTBP is very prevalent, it follows that the use of RSI in NTBP could be unsup- ported.

Key words: airway; non-traumatic brain patholo- gies; paramedic; rapid sequence intubation

PREHOSPITAL EMERGENCY CARE 2017; Early Online: 1–9

Received January 1, 2017 from Monash University, Department of Community Emergency Health and Paramedic Practice, Melbourne, Victoria, Australia (PFF, PAJ); Department of Epidemiology and Preventive Medicine, and Department of Community Emergency Health and Paramedic Practice Monash University, Melbourne, Victoria, Australia (KS); Discipline - Emergency Medicine University Western Australia, Perth, Western Australia, Australia (KS); Ambulance Victoria, Research and Evaluation, Victoria, Australia, Melbourne, Victoria, Australia (SB); Griffith University, School of Medicine, Brisbane, Queensland, Australia (MB); Monash Emergency Research Collaborative, Clinical Sciences at Monash Health, Monash University, Melbourne, Victoria, Australia (GB); Monash Medical Centre, Emergency Program, Monash Health, Melbourne, Victoria, Australia (GB); Royal Melbourne Hospital, Department of Emergency Medicine, Melbourne, Victoria, Australia (JK); Austin Health, Department of Emergency Medicine, Heidelberg, Victoria, Australia (MR); Peninsula Clinical School, Central Clinical School and Peninsula Health Emergency Medicine, Monash University, Melbourne, Victoria, Australia (PR); St. Vincent's Hospital, Emergency Medicine, Melbourne, Victoria, Australia (MRA); Revision received April 26, 2017; accepted for publication April 26, 2017.

Supplemental data for this article can be accessed on the publisher's website.

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doi: 10.1080/10903127.2017.1325952

Introduction

Rapid sequence intubation (RSI) is a process that utilizes sedative and paralytic drugs to facilitate the placement of an endotracheal tube. Rapid sequence intubation is used in a number of emergency medi- cal services (EMS) worldwide, including Australia,[1] numerous European countries,[2] South-Africa,[3] and in much of the United States.[4] Rapid sequence intubation in traumatic brain injuries has been the focus of research in the last two decades. In a trial in San Diego, prehospital head injured patients who underwent paramedic RSI were compared to a matched historical control group and survival outcomes compared. Mortality was increased in the RSI cohort compared with controls (33.0% versus 24.2%, $p < 0.05$).[5] However, a more recent randomized controlled trial conducted in Australia contradicted the San Diego trial. This trial suggested favorable neurological outcome at six

months for paramedic RSI, compared to in-hospital RSI (RR 1.28; 95% CI 1.00–1.64; P = 0.046).[1]

Rapid sequence intubation is not only used in the prehospital setting for head injuries and trauma. Bernard et al. from Victoria, Australia found that 49% of all RSIs in their emergency medical service (EMS) are on patients with a non-traumatic coma such as stroke and seizures (based on paramedic diag- nosis).[6] Non-traumatic brain pathologies (NTBP) is defined as an acquired brain injury (either permanent or transient) that includes brain tumors, meningitis, encephalitis, hypoxic/anoxic brain injury, stroke, arteriovenous malformations, tumors, aneurysms, brain hemorrhage, as well as brain injury due to diabetes, seizures and toxicity, metabolic conditions and alcohol and drug overdose.[7–9] While the prevalence of RSI for non-traumatic *coma* has been examined, the prevalence and survival outcomes for NTBP patients receiving paramedic RSI needs quantification. It is not clear that the evidence of effectiveness of RSI in traumatic injuries applies to NTBP, since NTBP is a heterogeneous group of pathologies and differs considerably from traumatic brain injuries in their pathophysiology.[10] Additionally, if NTBP is common in those that receive RSI then it is possible that no proof of benefit exist for a sizable proportion of RSI patients. Therefore, this study aims to quantify NTBP prevalence and survival as well as factors that predict mortality in a cohort of out-of-hospital RSI by EMS in Victoria, Australia.

METHODS

Study Design

A retrospective cohort study of NTBP cases in Victoria, Australia.

Setting

This cohort consisted of patients that had received RSI from Mobile Intensive Care Ambulance (MICA) Paramedics in Victoria and were transported to seven Melbourne-based hospitals for the period January 1, 2008 to December 31, 2015. Victoria is Australia's second most populous state with an area of 237,629 km^2 and Melbourne is the capital with a population of 4.6 million persons. Victoria has a two tier EMS system with approximately 400 MICA Paramedics in addition to 3,000 Advanced Life Support (ALS) Paramedics.[6] MICA paramedics use RSI in patients with coma (Glasgow Coma Score ::: 9) aged ;::14 years and ŧ transport time is more than 10 minutes to the nearest emergency department, for both traumatic and non-traumatic coma.[6] Rapid sequence intubation training includes 24 hours of theoretical and manikin training and 16 hours experiential training in an operating room in addition to undergraduate and postgraduate instruction on advanced airway management. MICA paramedics undertake a one-day theoretical and practical reaccreditation examination annually. RSI medications used in NTBP include intravenous fentanyl, midazolam, atropine (for bradycardia), and suxamethonium. These drugs have significant impact on physiology and includes tachycardia (atropine), respiratory depression (fentanyl, midazolam), depressed level of consciousness (midazolam), and elevated potassium levels and increased intragastric pressure (suxamethonium).[11]

Data Collection

We collected data retrospectively from eight sites in Melbourne: Ambulance Victoria, Monash Med- ical Centre, Dandenong, Alfred, Royal Melbourne, Frankston, Austin and St. Vincent's hospitals. We included all cases of RSI for the period January 1, 2008 to December 31, 2015 from the Ambulance Victoria data warehouse. Included were patients with a hospital diagnosed NTBP and either aeromedical or road transport to participating Melbourne hospitals (Figure 1). Data extracted included prehospital interventions, medications, ambulance scene and travel time intervals, paramedic diagnosis, vital signs (observations) and demographics from Ambulance Victoria, and survival data from the hospitals. Hospital data included emergency department survival, demographics, and duration of mechanical ventilation and intensive care unit (ICU) length of stay.

Definitions

For the purpose of this analysis and for inclusion into the study, we defined NTBP based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD10-AM) codes from in-hospital records for an episode of care (Table S1). ICD10-AM codes for NTBP were grouped for the pathologies: hemorrhagic stroke, ischemic stroke, other types of stroke, neoplasms of brain, inflammatory brain diseases, anoxic/hypoxic brain injury, protracted seizures, toxicity and toxic encephalopathy, hydrocephalus, diabetic metabolic encephalopathy, and other miscellaneous encephalopathies.[9,10] Under "toxicity and toxic encephalopathy," we included all neurotoxic toxidromes that, at the very least, affected the functioning of the ascending reticular activating system or analogous structures to cause coma.[12] These pathologies were classified as NTBP if the brain injury was either permanent or transient. We excluded degenerative and congenital brain diseases; birth related trauma as well as cardiac arrest not in NTBP. ICD10-AM codes S06 - (intracranial injury) define traumatic intracranial brain injuries and did not form part of the NTBP cohort.

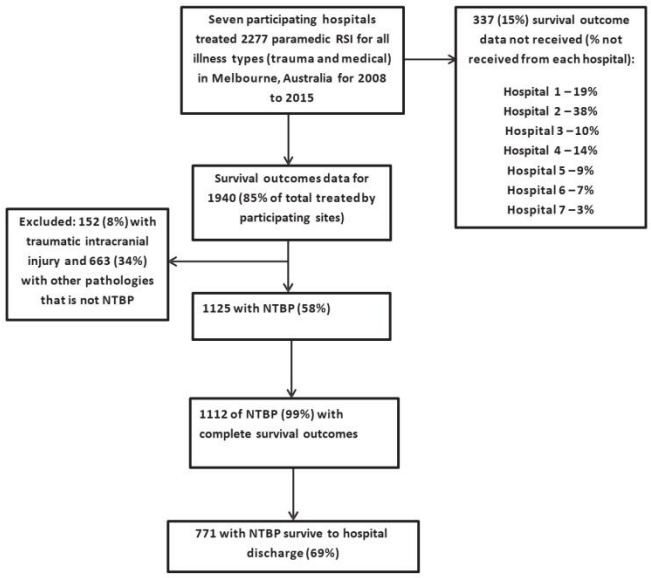

FIGURE 1. Patient selection for RSI in NTBP cohort.

However, we calculated the survival to hospital discharge of traumatic intracranial injuries to compare with NTBP.

Placement of endotracheal tube in the trachea beyond the vocal cords was confirmed using clini- cal means and/or end-tidal CO_2 waveform. Clinical confirmation supported by end-tidal CO2 waveform and defined intubation success. Duration of mechanical ventilation is the time in days on a ventilator in ICU, and ICU length of stay was the total time for each intensive care unit admission in days. The variable "prehospital time" was composed of three intervals, the response time of the emergency vehicle from time of call plus the time spent on scene plus transport to the hospital up the time of hospital arrival. The prehospital time interval served as a proxy for the time from injury until hospital interventions. We totaled the volume of crystalloid fluids (either sodium chloride or sodium lactate) as Ambulance Victoria switched from using mainly sodium lactate to sodium chloride in 2009.

Outcomes and Independent Variables

Out-of-hospital variables included demographic, date, scene and transport times, case description, vital signs (observations), paramedic-administered medications, dosages, and clinical procedures. In-hospital variables included demographic, date, ICD10-AM codes, duration of ICU stay, and mechanical ventilation status at separation from the emergency department and hospital. The primary outcome was survival to hospital discharge, derived from the separation disposition from in-hospital records. We accounted for comorbidities with a score by van Walraven (based on the Elixhauser index) derived from ICD 10-AM codes.[13]

Statistical Analysis

Stata version 14 (Stata Corp, College Station, Texas, USA) was used in this analysis. We calculated descriptive statistics for the outcomes variables and used a maximum likelihood-fitted logistic regression model for predictors of survival to hospital discharge. Variables were included in the initial baseline model if they were significant at $p < 0.20$ by the likelihood ratio test. After step-wise elimination of non-significant variables one-at-a-time, and then back-introduction, predictors only remained in the final multivariable model if they were significant at 5% level. A change in 20% of the magnitude of estimates was used to detect the presence of confounding.[14] We assessed the linearity of the logits of all continuous predictors in the multivariable model, and if there was a deviation from linearity, we fitted fractional polynomials to these non-linear terms.

We anticipated that certain variables might have a probability mass or "spike" at the zero value and such variables were modelled as a dichotomous variable plus a linear or non-linear term if appropriate. For

example, survival with certain medications and clinical interventions could "spike" at zero/no dose,[15] as those that had received no medications/interventions are likely to be qualitatively different than those who did receive the medications. Medication variables that take discrete values rather than being truly continuous were modelled as a categorical variable. For example, fentanyl is typically administered as 25, 50, or 100 micrograms with other doses used rarely. We adjusted estimates in the final multivariable model with an Elixhauser-Walraven score to account for comorbidity, and we scaled the score to avoid negative values. Walraven adapted the Elixhauser comorbidity index into a single score, which enables a more parsimonious adjustment in analysis.[13] We specified no interactions in the design and therefore none was tested. Goodness of fit of the final model was tested using the Hosmer and Lemeshow test.[14] We anticipated variation in survival between hospitals, however if intracluster correlation was low (less than 5%) for hospital survival then we did not use a multilevel model.[16] Results from logistic regression models are presented as odds ratios in tabular form. To maximize the sample size of this cohort, we included all cases of RSI from the RSI program inception to date.

Ethics

Alfred Hospital Ethics Committee provided overall ethics approval for this multisite cohort study. Research governance committees from each of the participating hospitals and Ambulance Victoria provided local approval.

RESULTS

The seven participating hospitals treated 2,277 patients that received paramedic RSI for all illnesses and indications from 2008 to 2015, and survival data was available for 1,940 (85%). Of the 1,940 complete survival dataset, 1,125 (58%) had at least one hospital-diagnosed NTBP diagnosis (Figure 1). For the 1,125 with NTBP, survival data was complete for 1,112 (99%), and no variable predicted missingness in the NTBP cohort. Twenty-two percent of all RSI patients with a NTBP had more than one instance of NTBP concomitantly, for a total number of 1,433 NTBP in 1,112 patients (Table 1). Common combinations of NTBP included 8% had an hemorrhagic stroke and hydrocephalus, 5% that had an ischemic and hemorrhagic stroke, 2% of NTBP had a malignant neoplasm and seizures, and 1.2% had a seizure and a hemorrhagic stroke together. Strokes were the most common, with 345 (24%) instances of hemorrhagic stroke, 151 (11%) ischemic stroke and 28 (2%) had a stroke that was not classifiable as either hemorrhagic or ischemic (Table 1). The second and third most common NTBP were toxicity/toxic encephalopathy and seizures, with 324 (23%) and 315 (22%), respectively. Our results indicate 69% of all of NTBP survived to hospital discharge, compared to 65% for traumatic intracranial injury. There was large variability in survival for the various NTBP, with hemorrhagic stroke the lowest at 31% and toxicity or toxic encephalopathy the highest survival to discharge at 98% (Table 1). Hemorrhagic stroke had 93% lesser odds of survival to hospital discharge, compared to other NTBP; OR = 0.07 (95% CI 0.05–0.09) and toxicity and toxic encephalopathy had almost 34 times the odds of survival; OR = 33.5 (95% CI 15.6–71.7) (Table 1).

Forty-three (4%) of all NTBP died in the emergency department. Furthermore, 49 (4%) of all NTBP admitted to hospital had an episode of cardiac arrest of which 62% survived to discharge. Table 2 presents univariable logistic regression results for demographic, clinical interventions, and observations. Multivariable logistic regression for strokes and seizures indicates that age is a predictor of survival to discharge, with decreased survival with increasing age (Table 3). Elixhauser-Walraven comorbidity score was associated with decrease in odds of survival for each additional point in a non-linear function across all multivariable analysis. For the 1,940 that received RSI for all indications (trauma and medical) and for whom

Table 1. Univariable logistic regression of NTBP that received paramedic RSI, predictors of survival to hospital discharge*

Type of NTBP	NTBP = 1433†	Survived = 771	Died = 341	Unadjusted OR (95% CI)	P-value
Anoxic brain injury	44 (3.1)	25 (56.8)	19 (43.2)	0.57 (0.30–1.05)	0.08
Encephalitis	29 (2.0)	26 (89.7)	3 (10.3)	3.47 (1.03–11.7)	0.02
Encephalopathy, other types	43 (3.0)	17 (39.5)	26 (60.5)	0.20 (0.11–0.41)	<0.001
Hemorrhagic stroke	345 (24.1)	106 (30.7)	239 (69.3)	0.07 (0.05–0.09)	<0.001
Hydrocephalus	94 (6.6)	38 (40.4)	56 (59.6)	0.26 (0.17–0.40)	<0.001
Diabetic metabolic encephalopathy	26 (1.8)	21 (80.8)	5 (19.2)	1.89 (0.70–5.05)	0.18
Ischemic stroke	151(10.5)	78 (51.7)	73 (48.3)	0.41 (0.29–0.58)	<0.001
Malignant brain neoplasm	26 (1.8)	24 (92.3)	2 (7.7)	5.46 (1.28–23.2)	0.003
Non-hemorrhagic/ischemic stroke	28 (2.0)	12 (42.9)	16 (57.1)	0.32 (0.15–0.69)	0.003
Seizures	315 (22.0)	296 (93.9)	19 (6.0)	10.7 (6.6–17.3)	<0.001
Toxicity and toxic encephalopathy	324 (22.6)	317 (97.8)	7 (2.2)	33.5 (15.6–71.7)	<0.001
Meningitis	8 (0.5)	6 (75.0)	2 (25.0)	1.11 (0.21–5.74)	0.90

*All non-missing data entries are expressed as percentages (in brackets).
† 1112 RSI patients had 1433 instances of NTBP.

Table 2. Univariable logistic regression of demographic, clinical interventions and observations in NTBP that received paramedic RSI, predictors of survival to hospital discharge*

Demographic factor	Survived (%)	Died (%)	Unadjusted OR (95% CI)	P-value
Age (years)†	47.1 (18.6)	67.6 (15.4)	0.94 (0.93–0.95)	<0.001
Sex				0.10
Male	439 (71.4)	176 (28.6)	1.0 (ref)	
Female	329 (66.7)	164 (33.2)	0.80 (0.62–1.04)	
Indeterminate	1 (100)	0 (0)	N/A	
Hospital				<0.001
1	82 (68.3)	38 (31.7)	1.0 (ref)	
2	38 (62.3)	23 (37.7)	0.77 (0.40–1.45)	
3	87 (85.3)	15 (14.7)	2.69 (1.37–5.24)	
4	158 (81.4)	36 (18.7)	2.03 (1.20–3.44)	
5	196 (63.1)	115 (36.9)	0.79 (0.50–1.24)	
6	168 (61.8)	104 (38.2)	0.75 (0.48–1.18)	
7	40 (80)	10 (20)	1.85 (0.83–4.09)	
Prehospital Clinical Interventions				
Airway suctioning	195 (72.4)	74 (27.5)	1.22 (0.90–1.65)	0.19
Crystalloid fluids (per 1000 mL)†	1.65 (0.89)	1.38 (0.75)	1.31 (1.14–1.52)	<0.001
Gastric tube	594 (70.1)	253 (29.8)	1.17 (0.87–1.57)	0.31
Endotracheal intubation success	751(69.2)	334 (30.7)	0.59 (0.20–1.82)	0.34
Fentanyl category (μg)				<0.001
:549	95 (83.3)	19 (16.7)	1.0 (ref)	
50 to 99	360 (60.0)	237 (39.7)	0.30 (0.18–0.51)	
:::100	314 (78.7)	85 (21.3)	0.74 (0.43–1.28)	
Maximum midazolam/morphine infusion rate (mg/h)‡	5 (5,7.5)	5 (5,5)	1.06 (1.03–1.10)	<0.001
Metoclopramide total (mg)‡	10 (10,10)	10 (10,10)	0.97 (0.92–1.03)	0.37
Oropharyngeal airway	394 (68.5)	181 (31.4)	0.92 (0.71–1.19)	0.54
Pancuronium category (mg)				<0.001
0	340 (81.1)	79 (18.9)	1.0 (ref)	
4 to 16	330 (61.0)	211 (39.0)	0.37 (0.27–0.49)	
:::16	99 (66.0)	51 (34.0)	0.45 (0.29–0.68)	
Total midazolam bolus (mg)‡	10 (6,15)	6.5 (4.5,10)	1.09 (1.06–1.11)	<0.001
Total midazolam/morphine infusion bolus (mg)‡	5 (2.5,10)	2.5(2.5,7.5)	1.04 (1.01–1.07)	<0.001
Suxamethonium category (mg)				0.18
:599	44 (67.7)	21 (32.3)	1.0 (ref)	
100–124	156 (64.7)	85 (35.3)	0.88 (0.49–1.56)	
125–149	341 (72.5)	129 (27.5)	1.26 (0.72–2.20)	
150	228 (68.5)	105 (31.5)	1.04 (0.59–1.83)	
Observations				
Final $ETCO_2$(mmHg)†	37.1 (7.8)	36.1 (6.7)	1.02 (0.99–1.04)	0.05
Final Glasgow Coma Scale score‡	3 (3,3)	3 (3,3)	1.06 (0.94–1.20)	0.32
Final pulse rate (p/min)†	98.8 (20.5)	99.4 (22.9)	0.99 (0.99–1.01)	0.63
Final respiratory rate (p/min)†	15.7 (4.7)	15.3 (4.7)	1.01 (0.99–1.03)	0.13
Final SpO_2 (%)‡	100 (99,100)	100 (99,100)	1.04 (1.00–1.07)	0.02
Final systolic blood pressure (mmHg)†	127.3 (23.9)	147.2 (33.1)	0.97 (0.97–0.98)	<0.001
Elixhauser-Walraven score‡	16.1 (7.3)	14.9 (6.7)	1.02 (1.00–1.04)	0.03
ICU length of stay (24 hours)†	2.4 (1.3,4.9)	2.1(0.9,4.7)	1.08 (1.03–1.11)	<0.001
Initial Glasgow Coma Scale‡	4 (3,8)	5 (3,7)	0.99 (0.96–1.03)	0.81
Initial pulse rate (p/min)†	100.9 (29.4)	88.8 (27.1)	1.01 (1.01–1.02)	<0.001
Initial respiratory rate (p/min)†	17.7 (7.8)	19.1 (7.2)	0.98 (0.97–0.99)	0.04
Initial SpO_2 (%) ‡	97 (91,99)	97 (92,99)	0.99 (0.98–1.01)	0.31
Initial systolic blood pressure (mmHg)†	134.4 (39.8)	164.4 (45.4)	0.98 (0.98–0.99)	<0.001
Maximum pulse rate (p/min)†	117.9 (24.6)	115.6 (25.8)	1.00 (0.99–1.01)	0.16
Maximum blood sugar level (mmol/l)	41 (71.9)	16 (29.1)	1.04 (0.57–1.90)	0.12
1.2 to 4.99	506 (71.1)	206 (28.9)	1.0 (ref)	
5–9.99	133 (61.9)	82 (38.1)	0.66 (0.47–0.91)	
10–14.99	37 (71.2)	15 (28.9)	1.01 (0.54–1.86)	
15–19.99	9 (60.0)	6 (40.0)	0.61 (0.21–1.74)	
:::20				
Maximum $ETCO_2$(mmHg)‡	46.1(13.0)	43.32 (11.3)	1.02 (1.00–1.03)	<0.001
Maximum Glasgow Coma Scale‡	6 (3,8)	6 (4,8)	1.03 (0.99–1.07)	0.12
Maximum respiratory rate (p/min)‡	21.2 (7.8)	21.4 (6.9)	1.00 (0.99–1.02)	0.77
Maximum SpO2 (%)‡	99.4 (1.7)	99.3 (3.1)	1.03 (0.97–1.09)	0.30
Maximum systolic blood pressure (mmHg)‡	160.4 (35.3)	191.2 (40.1)	0.98 (0.97–0.98)	<0.001
Mechanical ventilation (days)‡	0.92 (0.5,2.7)	1.7 (0.75,3.8)	1.01 (0.97–1.05)	0.57

(*Continue on next page*)

Table 2. Continued

Demographic factor	Survived (%)	Died (%)	Unadjusted OR (95% CI)	P-value
Minimum blood sugar level (mmol/L)				0.22
:51.2	8 (57.4)	6 (42.9)	1.0 (ref)	
1.2–4.99	59 (74.7)	20 (25.3)	2.21 (0.68–7.16)	
5–9.99	499 (70.5)	209 (29.5)	1.79 (0.61–5.22)	
10–14.99	121 (62.4)	73 (37.6)	1.24 (0.41–3.72)	
15–19.99	31 (70.4)	13 (29.6)	1.79 (0.52–6.12)	
;::20	8 (61.5)	5 (38.5)	1.20 (0.26–5.59)	
Minimum $ETCO_2$(mmHg)‡	33.9 (8.3)	32.6 (6.2)	1.02 (1.00–1.04)	0.02
Minimum Glasgow Coma Scale‡	3 (3,3)	3 (3,3)	1.05 (0.91–1.21)	0.47
Minimum pulse rate (p/min)†	83.9 (23.4)	76.5 (23.8)	1.01 (1.00–1.02)	<0.001
Minimum respiratory rate (p/min)‡	12 (10,16)	12 (12,16)	0.99 (0.97–1.01)	0.20
Minimum SpO_2 (%)†	91.4 (11.4)	91.3 (12.7)	0.99 (0.99–1.01)	0.94
Minimum systolic blood pressure (mmHg)†	107.3 (26.9)	126.9 (34.3)	0.98 (0.97–0.98)	<0.001
Cardiac arrest	30 (61.2)	19 (38.8)	0.68 (0.38–1.24)	0.22
Response time†	38.8 (29.2)	39.5 (30)	0.99 (0.99–1.00)	0.71
Scene time†	77.2 (24.9)	75.9 (20.0)	1.00 (0.99–1.00)	0.39
Transport time†	39.0 (23.4)	37.0 (20.3)	1.00 (0.99–1.00)	0.20
Prehospital time (total, minutes)‡	154.9 (43.6)	152.5 (37.9)	1.00 (0.99–1.00)	0.28

*All non-missing data entries for are expressed as percentages, except for means and medians indicated with: †mean (SD); ‡median (IQR). For observation variables, "initial" refers to first observed instance by paramedic during prehospital treatment, "final" refers to the last.

complete survival data were available, the prevalence of traumatic intracranial injuries was 152 (8%). The overall RSI intubation success proportion in this NTBP cohort is 98.3% with no evidence of a significant change in success over the eight year study period [χ^2 (DF = 7) = 3.9, p = 0.79]. Of the 468 RSI patients that had at least one kind of hospital-diagnosed stroke, paramedics were able to correctly classify these as having had a stroke in 299 cases (64%), and classi- fied most of the rest of strokes (31%) as non-specific or undiagnosed unconsciousness. After adjustment in the multivariable model, survival did not vary between hospitals and the intraclass correlation coefficient for the correlation of survival within hospitals was 0.002. Consequently, we did not adjust for hospital survival clustering.

LIMITATIONS

The data collected for all RSI (NTBP and all other pathologies) from the seven participating hospitals had 15% missing survival outcomes, but only 1% of the NTBP had missing survival results. It is clear that data collection for NTBP was more complete than for other illnesses. It is possible that the 1% with missing survival outcomes was systematically different from this cohort causing possible bias, despite our analysis showing that no variable predicts missingness in NTBP. As such, we believe our results are robust and relatively free of non-response bias. We did not describe the 34% that received RSI for other indications (not NTBP), as it was unfeasible given the large number of ICD10-AM that encodes these other indications. The purpose of this study is to enumerate NTBP only. There is a lack of a consistent definition of NTBP across the published research.[10] Therefore, the NTBP prevalence might differ somewhat if another definition is used. Even so, we believe our ICD10-AM based definition to be reasonable and it is in accordance with the literature.[7-10] Survival to discharge of NTBP will depend on the prevalence of various illnesses that comprise NTBP. For example, if a region has more strokes than reported in this study, the survival might be less than the proportion reported here and we caution against extrapolating our results to other regions that might have a different composition of NTBP.

We only adjusted for comorbidities, but not for the illness severity with a designed-for-purpose score, as illness severity indices were not available for most NTBP. Nonetheless, we have accounted for illness severity with the Glasgow Coma Scale as it is similarly predictive of in-hospital mortality in strokes as NIHSS,[17] FOUR,[18] and APACHE II.[19] Inaccurate coding of ICD10-AM might have caused bias in the period prevalence of NTBP in this cohort. We did not construct separate models for all eight of the NTBP due to sample size limitations for some. We also accounted for comorbidities in our multivariable model with the Elixhauser-Walraven score, to lessen any imbalances in comorbidities across groups. It is important to ensure that comparison groups are similarly sick, as maldistributions of prognosis can seriously bias results from observational studies.[20,21] In this analysis, those with a Walraven-Elixhauser score of less than 10 had 100% survival to discharge and this explains the very low survival odds of the higher scores as they are relative to these low scores with perfect survival. In addition, a slight rise and subsequent drop in survival is appar-

Table 3. Multivariable logistic regression of prehospital predictors of survival to hospital discharge for RSI strokes, seizures, and toxic encephalopathy

Factor	Adjusted OR (95% CI)	P-value
HEMORRHAGIC STROKE ($N = 345$)		
Age (years)	0.96 (0.94–0.98)	0.001
Elixhauser-Walraven score*		<0.001
5	1.00 (ref)	
10	0.0008 (0.001–0.06)	
20	0.002 (0.001–0.13)	
30	0.008 (0.001–0.53)	
40	0.007 (0.001–3.60)	
Concomitant ischemic stroke	2.57 (1.12–5.90)	0.03
Mechanical ventilation (days)	1.15 (1.06–1.25)	<0.001
Concomitant seizures	44.6 (5.00–394.7)	0.001
Maximum systolic blood pressure (mmHg)	0.99 (0.98–0.99)	0.005
Concomitant other encephalopathy types	0.02 (0.002–0.14)	<0.001
ISCHEMIC STROKE ($N = 151$)		
Age (years)	0.96 (0.93–0.98)	0.002
Elixhauser-Walraven score*		<0.001
5	1.00 (ref)	
10	0.01 (0.001–0.63)	
20	0.04 (0.001–2.43)	
30	0.02 (0.001–1.75)	
40	0.01 (0.001–2.64)	
ICU stay	2.48 (0.92–6.67)	0.07
Concomitant seizures	7.39 (1.56–34.8)	0.01
Initial GCS	1.18 (1.02–1.36)	0.02
Concomitant other encephalopathy types	0.02 (0.001–0.40)	0.012
SEIZURES ($N = 316$)		
Age (years)	0.95 (0.92–0.99)	0.007
Mechanical ventilation (days)†		0.001
1	1.00 (ref)	
5	0.40 (0.19–0.87)	
10	0.39 (0.18–0.87)	
20	0.38 (0.17–0.86)	
Elixhauser	0.99 (0.91–1.07)	0.85
Concomitant other encephalopathy types	0.13 (0.03–0.60)	0.008
TOXICITY AND TOXIC ENCEPHALOPATHY ($N = 324$)		
Mechanical ventilation (days)‡		0.01
1	1.00 (ref)	
5	0.16 (0.02–1.55)	
10	0.13 (0.01–1.65)	
20	0.11 (0.007–1.69)	
Elixhauser	0.88 (0.78–0.98)	0.02
Concomitant anoxic injury	0.10 (0.02–0.73)	0.02

*Elixhauser score fitted as fractional polynomial terms β_1 (Elixhauser+1/10)^3 + β_2 (Elixhauser+1/10)^3 ln + β_3 (Elixhauser+1/10)^3 ln^2 + β_4 (Elixhauser+1/10)^3 ln^3.
†Mechanical ventilation fitted as fractional polynomial terms β_1 (Mechanical ventilation/10)$^{-2}$ β_2 (Mechanical ventilation/10)$^{-2}$ ln.
‡Mechanical ventilation fitted as fractional polynomial terms: β_1 (Mechanical ventilation+0.04/10)$^{-1}$.
Variables included in multivariable were only those that were significant at the 5% level.

ent for middle-range Walraven-Elixhauser scores. We believe that this rise is likely due to coding bias, where comorbidities are under-recorded in the acutely ill (such as NTBP) compared to illness that are less acute.[22] It is likely that an increased capture of ICD10-AM codes the longer a patient stays in hospital, which leads to an association between higher scores and increased survival. An additional analysis shows a 0.34 (95% CI 0.25–0.44) point rise for each extra day a patient spends in ICU, suggesting coding bias. All of the NTBP in this study had the potential to cause acute illness, and we believe it is likely that the NTBP recorded for each admission was related to the decision to use RSI but cannot be guaranteed, as it is not always possible to know which NTBP caused RSI, especially in those with multiple concomitant NTBP.

DISCUSSION

Our results revealed that 58% of paramedic RSI was on patients with a hospital-diagnosed NTBP, compared to 8% of all RSI patients with a traumatic intracranial injury. It is evident that NTBP is much more common than traumatic brain injuries among those that receive paramedic RSI in Victoria, Australia. Our results showed a higher prevalence compared to the Bernard et al. study, as our results were derived from in-hospital diagnosis, compared to Bernard, which based their esti-

mates on paramedic diagnosis of NTBP.[6] Survival to hospital discharge for NTBP was 4% higher than those diagnosed with a traumatic intracranial injury (69% versus 65%), although there is a large variation in survival among the NTBP. Strokes were the most common NTBP, and had poor survival, which is consistent with other stroke studies.[23,24] Other common NTBP were seizures and toxicity/toxic encephalopathies (alcohol, drug medication, or other chemical overdoses and exposures), which had high survival. Furthermore, and keeping in mind that this study was not powered for this purpose, our results showed no evidence of a beneficial or harmful effect of any paramedic administered medications or clinical interventions after adjustment for other covariates. Additionally, no prehospital time interval predicted survival in the group of NTBP or in any subgroup analysis, which is surprising considering that timeliness to treatment is important, especially in strokes.[25] Since this NTBP cohort consists mainly of a subset of stroke patients with very high mortality and toxicity and seizures with very low mortality, it could be that the prognostic risk in this cohort is powerful enough to negate any impact of rapid paramedic transport. Factors that did predict survival include Glasgow Coma Scale (GCS), duration of mechanical ventilation, age, ICU length of stay, and comorbidities.

The results from this study showed that NTBP are seven times more prevalent than traumatic intracranial injuries in patients that receive RSI in Victoria, Australia. Even so, there is no high quality evidence to justify RSI in NTBP. A secondary outcome of the Bernard et al. randomized controlled trial showed that RSI by paramedics in head trauma increases the rate of favorable neurologic outcome at 6 months compared with intubation in the hospital.[1] However, it is not clear that this evidence can be generalized to NTBP. Hypoxia, hypo/hypercapnia,[26] hyperventilation,[27] hypotension,[28] hypertension following laryngoscopy,[29] and aspiration[30] are potential mechanisms of increased mortality in RSI following traumatic intracranial brain injury. Nevertheless, it is possible that the mechanisms through which RSI might influence mortality in traumatic brain injuries will not be the same as in NTBP. Laryngoscopy raises intracranial pressure (ICP) in head trauma, which could worsen an already elevated ICP.[29] It is not clear if laryngoscopy is similarly problematic in NTBP such as seizures and toxidromes that are not usually characterized by pronounced rises in ICP. Moreover, it is known that mechanical ventilation increases intrathoracic pressures, which in turn decreases cardiac output.[31] Furthermore, since myocardial dysfunction is commonplace in subarachnoid hemorrhage,[32] and given that positive pressure ventilation can decrease cardiac output, it follows that ventilation after RSI could decrease cardiac output in SAH. If RSI can cause a decrease in cardiac output in SAH, perhaps it could do so for other types of stroke and NTBP. On the other hand, a recent prospective study found no association between *traumatic brain injury* and myocardial dysfunction, in contrast to SAH.[32] It makes sense that positive pressure ventilation after RSI could affect mortality differently when comparing head trauma and NTBP. These two examples suggest some mechanisms though which RSI can have different mortality and morbidity when comparing traumatic brain injury to NTBP. Given the evidence of RSI in head trauma might not apply to NTBP, and considering our results show that NTBP is much more prevalent than TBI, it is possible that RSI is without an evidence basis in many instances.

This data enabled the analysis of four subgroups: ischemic and hemorrhagic strokes, seizures, and toxicity/toxic encephalopathy. Remarkably, concomitant seizures in those patient with hemorrhagic stroke was associated with increased survival, despite seizures being a predictor of mortality,[33] but others found increased survival similar to our results.[34] Concomitant ischemic stroke and hemorrhagic stroke showed a two-and-half times increased odds of survival, compared to hemorrhagic stokes only, and this finding remains unexplained. We speculate that in this group of RSI patients, which have a high stoke mortality, this finding could be an artefact of illness severity.

CONCLUSIONS

This analysis shows that non-traumatic brain pathologies are seven times more prevalent than traumatic brain injuries in patients that receive out-of-hospital RSI in Victoria, Australia. Since the mechanisms through which RSI impact mortality might differ between traumatic brain injuries and NTBP, and given that NTBP is ubiquitous, it follows that the use of RSI in NTBP could be unsupported. As such, there is a requirement for high quality observational research or a controlled trial that compares outcomes for RSI to no RSI in NTBP.

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*See Appendix C, Tables C1.2 for the supplementary material

3.4 Principle findings and conclusions

This cohort study showed that 58% of the 1,940 patients who received RSI had at least one hospital-diagnosed NTBP, and 69% all of NTBPs survived to hospital discharge. Stroke was the most common pathology that had generally poor survival to discharge at 37%, compared to the second most common NTBP (toxicity/toxic encephalopathy) at 98%. No out-of-hospital clinical intervention or prehospital time interval predicted survival significantly. Factors that did prove indicative include the GCS, duration of mechanical ventilation, age, ICU length of stay and comorbidities. Evident from this cohort of RSI patients, NTBPs are very common. Despite their prevalence, no high-quality evidence that supports RSI is currently available. Hence, this paper emphasises that a randomised trial or quality observational study is urgently needed.

Chapter 4: Association of paramedic RSI and survival in out-of-hospital stroke

4.1 Declaration for Chapter 4

4.1.1 Monash University

Fouche PF, Smith K, Jennings PA, Boyle M, Bernard S. The association of paramedic rapid sequence intubation and survival in out-of-hospital stroke. *Emerg Med J* [Internet] 2019; **36**(7): 416–22. Available from: https://emj.bmj.com/content/36/7/416.long doi: 10.1136/emermed-2019-208613[1]

4.1.2 Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work were the following:

Nature of contribution	Extent of contribution (%)
Lead author responsible for data collection, statistical analysis and manuscript preparation. Responsible author who accepts overall responsibility for publication.	90%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated.

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Paul Jennings	Manuscript preparation	–
Malcolm Boyle	Manuscript preparation	–
Karen Smith	Manuscript preparation, data collection	–
Stephen Bernard	Manuscript preparation	–

4.2 Background and context

Although paramedics practise RSI to secure patient airways in cases of stroke,[1-3] the only high-quality evidence to support its use derives in one out-of-hospital RCT of TBIs.[39] Importantly, brain trauma differs from stroke, so it is not clear that the evidence from this head injury trial can be extrapolated to NTBP.[3] Urgency for evidence that support NTBP RSI has increased following the systematic review in Chapter 1, which demonstrated how intubation is commonly used in seizure, overdose and poisoning, and stroke.[2] Not only is RSI frequently employed in NTBPs, but stroke is the most prevalent condition in patients that receive paramedic RSI (further demonstrated in the researcher's own recent cohort study).[3] The systematic review also showed that almost 80% of haemorrhagic strokes receive intubation and ischaemic stroke anywhere from 6–25% through methods such as RSI.[2] Further noted, stroke is the most common NTBP in RSI recipients with the highest mortality rate—especially if haemorrhagic in nature.

Since strokes are most commonly intubated using RSI and have the highest mortality, generating evidence to support (or contest) stroke RSI is critical. Ideally, an RCT would provide the best quality evidence, but many obstacles, including gross financial expense and time required for completion, impede its viability. In the absence of a trial, observational studies can be used to generate estimates of treatment effects.[56,57]

4.3 Aims of this research

This section presents the results of a cohort study published in the *Emergency Medicine Journal* under the title 'The association of paramedic rapid sequence intubation and survival in out-of-hospital stroke'.[1] Essentially, it aimed to compare the survival-to-hospital discharge of a sample group that received paramedic RSI for strokes against another that did not. This study was based on all strokes RSI conducted in Victoria by paramedics for a full decade.

This large data-linkage study utilised a total of 38,352 complete stroke observations (including 782 RSIs) to predict propensity scores through a boosted logistic regression model. Propensity score methods are efficient at reducing bias in observational research.[58-60] Since haemorrhagic strokes had poorer prognosis than ischaemic strokes, the large number of

haemorrhagic strokes in the RSI group could bias results in favour of no-RSI. To counter imbalances between the RSI and no-RSI groups, the analysis used propensity score matching. Ideally, an RCT would be employed to compare RSI to no-RSI, as this is the most reliable method of ensuring that confounding factors are equalised between treated and control groups. When a trial is not easily conducted, observational research using propensity score methods can instead be used. As propensity score matching attempts to emulate features of an RCT, the technique was applied to create a matched dataset, with a multilevel logistic regression estimating the treatment effect of RSI. The results were tested for robustness for missing data and to gauge the effects of unmeasured confounding due to illness severity. Appendix C.3 contains figures that show the causal directed acyclic graph and distribution of propensity scores referred to in the publication of this chapter. Appendix C.4 is a response to a letter to the editor in comment of this publication.

The association of paramedic rapid sequence intubation and survival in out-of-hospital stroke

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/emermed-2019-208613).

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Received 26 March 2019
Revised 4 May 2019
Accepted 10 May 2019

To cite: Fouche PF, Smith K, Jennings PA, *et al*. *Emerg Med J* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/emermed-2019-208613

AbsTrACT

Introduction Ambulance transport of patients with stroke is common, with rapid sequence intubation (RSI) to secure the airway used regularly. Randomised controlled trial evidence exists to support the use of RSI in traumatic brain injuries (TBIs), but it is not clear whether the RSI evidence from TBI can be applied to the patient with stroke. To this end, we analysed a retrospective stroke dataset to compare survival of patients with RSI compared with patients that did not receive RSI.

Methods This study was a retrospective analysis of 10 years of in-hospital and out-of-hospital data for all patients with stroke attended by Ambulance Victoria, in Victoria Australia. Generalised boosted logistic regression was used to predict propensity scores, with initial vital signs, age and demographic variables as well as measures of illness severity and comorbidity included in the prediction model. This analysis employed a 1:1 nearest-neighbour matching which was applied to generate a dataset from which we calculated the OR of survival to hospital discharge of patients receiving RSI versus no-RSI. The sensitivity of these results to unmeasured confounding was assessed with deterministic sensitivity analysis.

results The propensity score-matched cohort showed a decreased survival for RSI in strokes with an OR 0.61 (95% CI 0.45 to 0.82; p=0.001) when compared with no-RSI. A subgroup analysis showed no significant survival difference for ischaemic strokes: OR 0.66 (95% CI 40 to 1.07; p=0.09). The survival for haemorrhagic stroke was OR 0.60 (95% CI 0.41 to 0.90; p=0.01) lesser for RSI. Results were likely robust to unmeasured confounding and missing data.

Conclusions Our retrospective analysis shows a decrease in survival when RSI is utilised by paramedics for stroke. Since RSI is commonly used for strokes, controlled trial evidence to support this practice is urgently needed.

Key messages

What is already known on this subject

► Rapid sequence intubation (RSI) is used by paramedics to secure the airway in strokes. The only evidence to support such use is an out-of-hospital randomised controlled trial of traumatic brain injuries. Brain trauma differ from stroke, and it is not clear that the evidence from this head injury trial can be extrapolated to stroke.

What this study adds

► This propensity score-matched cohort study of out-of hospital RSI by paramedics is the first to show decreased survival for RSI in strokes. Furthermore, this study demonstrates a considerably larger decrease in systolic blood pressure for those that receive RSI, compared with no-RSI. Additional derangements in carbon dioxide, oxygen, pulse rate and respiratory rate found here could explain this decreased survival in stroke.

InTrOduCTIOn

Strokes accounts for 10% of deaths worldwide,[1] and almost 5% of all disability adjusted life years. Rapid sequence intubation (RSI) is a commonly used procedure to secure the airway in patients with stroke that uses sedative and paralytic drugs to facilitate endotracheal intubation. It is not clear what proportion of out-of-hospital strokes receive RSI, but Meyer *et al* reported that 55% of their out-of-hospital haemorrhagic strokes received RSI.[2] The Meyers study suggests that RSI use might be high in haemorrhagic strokes, but it is not known how common strokes are in those that receive RSI. A recent Australian out-of-hospital study showed that strokes form a substantial proportion (36.6%) of RSI undertaken by paramedics.[3]

While RSI is commonly used by paramedics in stroke, no high-quality evidence for RSI in stroke currently exist.[3] An out-of-hospital randomised trial that compared paramedic RSI for traumatic head injury showed favourable neurological outcome compared with in-hospital RSI.[4] However, it is not clear that the evidence from this trial can be generalised to strokes, as there are significant differences between patients with the stroke and traumatic brain injury (TBI). One such difference is the impact of mechanical ventilation. Mechan- ical ventilation accompanies intubation and could decrease cardiac output. For example, intracranial haemorrhages frequently have decreased cardiac output, which is less typical in brain trauma.[5] This suggests that mechanical ventilation after Intubation could influence survival differently when TBI is compared with strokes because of this difference in cardiac output. On average, TBIstroke. Since age is associated with increased mortality from nosocomial infections after mechanical ventilation,[6] and keeping in mind that strokes tend to be older than

patients with TBI, intubation in RSI could cause more infections in stroke compared with brain trauma.

If the evidence from brain trauma cannot be used as a basis for stroke airway management, then research to justify stroke RSI is needed. The objective of this study to analyse a retrospective stroke dataset to compare survival of patients with stroke who received RSI compared with patients that did not receive RSI by paramedics.

MeThOds

study setting and data sources

Victoria has nearly 6.5 million residents serviced by a single two-tier emergency medical service, Ambulance Victoria. The two tiers consist of Mobile Intensive Care Paramedics (MICA) and advanced life support paramedics. Only MICA paramedics are authorised to provide RSI to patients that have a Glasgow Coma Scale (GCS) of less than 10 due to head trauma, non-TBIs, respiratory failure, severe hyperthermia, severe uncontrolled pain and airway burns.[7] Suxamethonium is the primary paralytic, with pancuronium used to maintain paralysis. Midazolam, morphine/midazolam infusions, atropine, ketamine and fentanyl are available to assist RSI.[7]RSI is authorised when transport time is more than 10 min to the nearest suitable emergency department. This study analysed data from 131 hospitals and clinics in Victoria, Australia from the 10-year period: 1 January 2008 to 31 December 2017. The Centre for Victorian Data Linkage provided all in-hospital patient records via the Victorian Admitted Episodes and Victorian Emergency Minimum dataset and Ambulance Victoria provided all out-of-hospital data. In-hospital and out-of hospital datasets were merged using deterministic linkage. Monash University Human Research Ethics Committee gave ethics approval for this study (Ref. No. 8618).

selection of study cohort

This study included all patients of any age that were treated and transported by Ambulance Victoria, with a final hospital diagnosis of stroke. We excluded all cases with traumatic intracranial injury, transient ischaemic attack and strokes that could not be classified as either haemorrhagic or ischaemic. Instances of stroke were identified by the Australian modification of ICD10 codes recorded for a particular episode of care, and incorporated codes: I60, I61, I62.9 and I63. These Tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD10) codes served as an operational definition of the strokes included in our cohort. We included all strokes, whether they were primary or secondary, for a particular episode of care. The Centre for Victorian Data Linkage selected all patients with stroke codes, regardless of ambulance transport or not. These patients with stroke were then linked to the Ambulance Victoria out-of-hospital dataset to select a cohort that had a stroke and were transported by ambulance.

Predictors and outcomes

The primary outcome was survival to hospital discharge, which is defined as the patient being discharged from hospital alive and is identified from the discharge disposition at hospital separation. Variables from in-hospital records and the Ambulance Victoria datasets served as potential predictors and include demographic, treatment, baseline observations, scene and transport time intervals, pathologies, length of stay and outcomes.

Prognostic risk influences the choice to use intubation, causing confounding by indication.[8] Previous work shows that illness severity and comorbidity are important confounders-by-indication in non-TBIs.[3] An effective way to account for confounding by indication is to use illness severity and comorbidity risk adjustment.[9] To account for comorbidity, we calculated and adjusted for the Walraven-Elixhauser score.[10] Illness severity was quantified using the GCS. While the GCS was not designed as a stroke severity score, it is similarly predictive of in-hospital mortality as National Institute of Health Stroke Scale (NIHSS) in patients with stroke.[11] To achieve proper risk adjustment, we added the Walraven-Elixhauser comorbidity score and the initial paramedic measured GCS in the propensity score model. We specified a priori that age, initial pulse rate, blood pressure, respiratory rate, GCS, SPO_2, blood glucose level, comorbidity, the year of RSI, sex and type of stroke were important predictors and these were included in our propensity prediction model if there were sufficient data (more than 90%). We did not adjust for any in-hospital treatments, as we believe that RSI can cause the likelihood of in-hospital interventions, and such adjustments would be on a mediator variable, which would introduce bias.[12] Selection of propensity score prediction variables was based on stroke literature and a causal directed acyclic graph (online supplementary figure S1).

definitions

Strokes are defined by ICD10-AM codes and we further subtyped strokes for ischaemic and haemorrhagic strokes. Ischaemic strokes include cerebral infarction and haemorrhagic strokes comprise subarachnoid heammorhage, intracerebral heammorhage and other intracranial non-traumatic heammorhage. RSI is defined as the attempted or successful placement of an endotracheal tube in the trachea after receiving a paralytic agent, with or without additional medications. Successful placement of endotracheal tube in the trachea was confirmed using clinical means and end-tidal CO_2 waveform. Hypotension was defined as a systolic blood pressure less than 90 mm Hg, and normocapnia as an end-tidal CO_2 of between 35 and 45 mm Hg. Hypoxia was defined as a SPO_2 reading of less than 90%.

statistical analysis

Stata V.14 (Stata Corp, College Station, Texas, USA) was used in this analysis. Categorical variables are presented as frequencies, and continuous variables as means with SD. Categorical variables were compared with the χ^2 test and continuous predictors with the t-test or Wilcoxon rank-sum test. Hypothesis tests were two-sided, with a significance level of $p<0.05$.

Propensity score matching

This analysis used propensity score matching to adjust for confounding bias. A generalised boosted logistic model was used to predict propensity scores. This boosted model implements the boosting algorithm described by Hastie, Tibshirani and Friedman, and is a re-interpretation of adaptive boosting, which was modified into the likelihood framework.[13] We performed a 1:1 nearest-neighbour match for each patient that had received RSI within a maximum calliper of 0.1 of the propensity score. The propensity matched sample was used to conduct a multilevel logistic regression to account for the clustering effect of matching and hospitals. All selected covariates were added to the fixed effect portion, and hospital was added as a random effect. All variables that were in the propensity score model were used in the logistic regression, and results are reported as ORs. Model fit of the analysis of the matched dataset was assessed with Hosmer and Lemeshow goodness-of-fit test, and the boosted model with pseudo-R^2. To assess the performance of

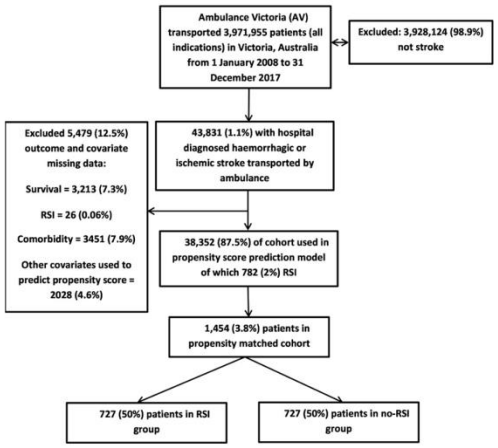

Figure 1 Patient selection for a cohort of RSI in stroke. RSI, rapid sequence intubation.

the propensity score matching, baseline and post-match variables were compared using standardised differences, where a difference less than or equal to 0.1 was considered insignificant. Furthermore, we compared RSI versus no-RSI for changes in systolic blood pressure, respiratory rate, pulse oximetry, GCS and pulse. These vital-sign changes were calculated by subtracting the final on-scene value from the first measurement on arrival.

sensitivity analysis

We deleted missing covariate observations for the propensity score prediction model and main analysis and compared these results to an analysis with imputed missing covariates. We did not impute survival or RSI itself. Additionally, we tested the robustness of the results to unmeasured confounding using a deterministic sensitivity analysis.[14] Previous research showed that a large source of unmeasured confounding is likely to be unaccounted for by illness severity.[15] Consequently, we calculated the impact on survival of 10% to 100% additional prevalence of unmeasured illness severity in the RSI group, compared with an extra 5% in the no-RSI group. Furthermore, we anticipated missing covariates, and we imputed missing data using multivariate normal regression for each covariate and treatment group separately. No imputations of survival were completed and were deleted from all analyses. We deleted missing covariate observations for the main analysis and compared these results to an analysis with imputed missing observations.

results

This cohort of stroke transported by ambulance included 43 831 patients in Victoria, Australia (figure 1) of which 882 (2.0%) received RSI. Baseline and in-hospital characteristics are compared in table 1. Of the 38 352 with complete data, 12 708 (33.1%) were diagnosed with haemorrhagic stroke and 26 996 (70.4%) with ischaemic stroke, with 1352 (3.5%) diagnosed with both stroke types. Of those who received RSI, suxametho- nium was utilised in 777 (99.4%) of patients and pancuronium in 631 (80.7%) of patients. Fentanyl was used in 750 (95.9%) of the cohort; ketamine in 20 (2.6%); midazolam in 752 (96.2%) and midazolam/morphine infusions in 627 (80.2%). The overall intubation success was 97.3% and first-pass success 89.4% with no significant change in success over time for overall (p=0.50 for trend) and first pass (p=0.07 for trend).

Table 1 Patient, demographic, prognostic and in-hospital factors in the full cohort of stroke

	Patients, no. (%)		
Characteristic	Total (n=38 352)	rsi (n=782)	no-rsi (n=37 570)
Demographic			
Age, mean (SD), years	73.0 (15.2)	65.2 (15.6)	73.1 (15.2)
Sex			
Male	19 662 (51.3)	382 (48.9)	19 280 (51.3)
Female	18 690 (48.7)	400 (51.2)	18 290 (48.7)
Illness			
Haemorrhagic stroke	12 708 (33.1)	581 (74.3)	12 127 (32.3)
Ischaemic stroke	26 996 (70.4)	244 (31.2)	26 752 (71.2)
Illness severity/comorbidity, mean (SD)			
Elixhauser comorbidity score*	20.8 (7.4)	18.1 (7.4)	20.8 (7.4)
Initial Glasgow Coma Scale	13.2 (3.0)	6.1 (3.3)	13.4 (2.8)
Observations, mean (SD)			
Initial pulse rate	83.2 (19.8)	88.3 (27.7)	83.1 (19.6)
Final pulse rate	81.9 (19.1)	99.0 (22.6)	81.6 (18.7)
Initial systolic blood pressure	151.1 (32.8)	162.6 (44.3)	150.8 (32.5)
Final systolic blood pressure	149.4 (30.1)	145.3 (32.2)	149.5 (30.0)
Initial respiratory rate	17.7 (4.8)	17.8 (7.9)	17.7 (4.7)
Final respiratory rate	17.1 (4.3)	12.0 (7.2)	17.2 (4.1)
Initial SPO_2	95.6 (5.6)	93.6 (10.5)	95.7 (5.3)
Final SPO_2	96.9 (3.6)	98.4 (4.6)	96.8 (3.6)
Ambulance time intervals, minutes mean (SD)			
Response time	19.7 (21.8)	15.7 (16.6)	19.8 (21.8)
Scene time	22.6 (14.2)	57.9 (25.0)	21.8 (12.9)
Transport time	24.0 (21.8)	29.8 (22.5)	23.9 (21.7)
Hospital			
Time in intensive care unit, mean (SD), hours	121.6 (164.5)	111.5 (137.6)	122.9 (167.5)
Mechanical ventilation in intensive care unit, mean (SD), hours	104.3 (153.6)	82.3 (112.4)	108.3 (159.5)
Hospital length of stay, mean (SD), days	9.1 (11.4)	10.1 (20.4)	9.1 (11.2)
Emergency department length of stay mean (SD), min	446.7 (332.6)	314.5 (234.6)	449.9 (334.0)
Year			
2008	3154 (8.2)	82 (10.5)	3072 (8.2)
2009	3480 (9.1)	82 (10.5)	3398 (9.0)
2010	3790 (9.9)	104 (13.3)	3686 (9.8)
2011	3879 (10.1)	94 (12.0)	3785 (10.1)
2012	3892 (10.2)	81 (10.4)	3811 (10.4)
2013	3860 (10.1)	69 (8.8)	3791 (10.1)
2014	3112 (8.1)	54 (6.9)	3058 (8.1)
2015	4092 (10.7)	56 (7.2)	4036 (10.7)
2016	4426 (11.5)	83 (10.6)	4343 (11.6)
2017	4667 (12.2)	77 (9.9)	4590 (12.2)

*Scaled to avoid negative values.
RSI, rapid sequence intubation.

Table 2 Baseline factors in a propensity score-matched cohort of stroke

Characteristic	Patients, no. (%) rsi (n=727)	no-rsi (n=727)	standardised difference
Demographic			
Age, mean (SD), years	65.8 (15.5)	65.6 (16.5)	0.01
Sex			0.04
Male	356 (49.0)	342 (47.0)	
Femal	371 (51.0)	385 (52.9)	
Illness			
Haemorrhagic stroke	527 (72.5)	536 (73.7)	0.03
Ischaemic stroke	241 (33.2)	219 (30.1)	0.07
Illness severity/comorbidity, mean (SD)			
Elixhauser comorbidity score*	18.3 (7.5)	18.3 (7.3)	0.001
Initial Glasgow Coma Scale	6.2 (3.4)	6.0 (3.1)	0.05
Observations, mean (SD)			
Initial pulse rate	88.5 (27.2)	89.1 (27.4)	0.02
Initial systolic blood pressure	160.2 (42.6)	159.3 (42.1)	0.02
Initial respiratory rate	17.9 (7.9)	18.2 (7.7)	0.04
Initial SPO_2	93.6 (10.6)	93.1 (10.6)	0.04
Year			
2008	73 (10.0)	77 (10.6)	0.02
2009	76 (10.5)	83 (11.4)	
2010	99 (13.6)	91 (12.5)	
2011	86 (11.8)	77 (10.6)	
2012	76 (10.5)	68 (9.4)	
2013	65 (8.9)	64 (8.8)	
2014	54 (7.4)	56 (7.7)	
2015	51 (7.0)	67 (9.2)	
2016	79 (10.9)	65 (8.9)	
2017	68 (9.4)	79 (10.9)	

*Scaled to avoid negative values.
RSI, rapid sequence intubation.

Overall outcomes

After deleting observations with missing data, the cohort comprised of 38 352 transported by ambulance with a stroke of which 30 926 (80.6%) survived to hospital discharge. In an unadjusted regression analysis those that had received RSI had lesser survival of OR 0.08 (95% CI: 0. 07 to 0.1; p<0.001) compared with those patients that did not receive RSI. Table 1 presents characteristics of the RSI versus no-RSI groups of the full cohort.

Propensity score-matched cohort

A total of 38 352 complete observations (including 782 RSI) were used to predict propensity scores with a boosted logistic regression model. The pseudo-R^2 for the boosted propensity score model was 0.56 for the training dataset and 0.38 for the test dataset, which indicates no overfitting. After a 1:1 match, the analysis cohort contained 1454 strokes with 727 RSI matched to 727 patients with non-RSI (figure 1). Baseline characteristics of the matched cohort are provided in table 2.

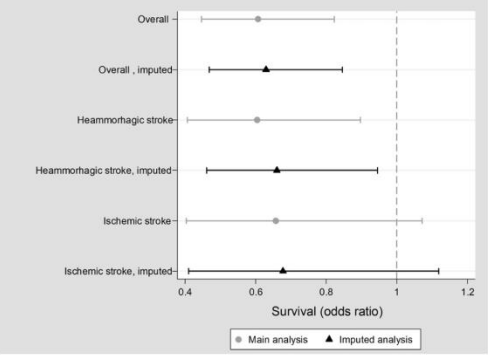

Figure 2 Survival of RSI versus no-RSI in strokes in a propensity matched cohort (dashed line at zero survival difference and with 95% CIs). RSI, rapid sequence intubation.

The patients were well matched on all relevant characteristics, and the distribution of propensity scores was similar between matched groups (online supplementary figure S2). A multilevel logistic regression analysis of the matched cohort shows that survival to hospital discharge was lower in the RSI group: OR 0.61 (95% CI: 0.45 to 0.82; p=0.001) (figure 2). This model had good fit: Hosmer-Lemeshow χ^2 (DF=8; p=0.16). This regression adjusted for all variables that were in the propensity score prediction model. We also added initial SPO_2 and initial blood glucose levels to this model, since there were few missing data for these two variables in the matched sample, even though there were too many missing to include these in the propensity score prediction model.

The mean time to intubation from arrival at the patients side was 44.1 min (SD=19.2) and time to intubation did not predict survival; OR 1.00 (95% CI: 0.99 to 1.02; p=0.54). The ratio of covariate variance between the RSI and no-RSI group in the matched sample is 1.13. A final end-tidal CO_2 reading of less than 35 mm Hg was present in 43.5% of patients that had received RSI; less than 25 mm Hg in 1.7% and higher than 45 mm Hg in 3.6%. Additionally, 12.1% of patients that received RSI had a minimum end-tidal CO_2 of less than 25 mm Hg. For patients that had received RSI, 1.7% had a final systolic blood pressure of less than 90 mm Hg, and 13.3% had a minimum systolic blood pressure of less than 90 mm Hg. A final SPO_2 of less than 90% was noted in 2.5%, and a minimum SpO_2 of less than 90% seen in 26.3% of patients that had received RSI.

We calculated the difference between the final and first measured systolic blood pressure, pulse rate, respiratory, GCS and oxygen saturation for all patients (table 3). In the matched cohort, the RSI group showed a larger decrease in systolic blood pressure than the non-RSI group, with a decrease that was more than twice as large as non-RSI. Oxygen saturation improved more in the RSI than no-RSI group. Respiratory rate was decreased almost six breaths a minute in those that received RSI, compared with those that did not. Furthermore, in the RSI group, the pulse rate change was almost 10 per minute increased, compared with no-RSI where there was a slight decrease in pulse rate. In the matched cohort those that had received RSI, 68 (9.4%) had pneumonia compared with 38 (5.2%) of the non-RSI: difference 4.1% (95% CI: 1.4% to 6.7%; p=0.002).

Table 3 Comparison of changes in vital signs in a propensity score-matched cohort of 1454 strokes

Change in vital sign*	rsi (mean; sd)	no-rsi (mean; sd)	difference (95% CI; p)
Systolic blood pressure (mm Hg)	−16.1 (40.6)	−6.4 (30.6)	9.7 (6.0 to 13.6; p<0.001)
SPO_2 (%)	4.9 (11.1)	3.6 (10.2)	−1.3 (−2.5 to −0.06; p=0.04)
Respiratory rate (per minute)	−5.9 (9.4)	−0.2 (5.8)	5.6 (4.8 to 6.5; p<0.001)
Glasgow Coma Scale (unit)	−2.8 (3.3)	0.9 (3.0)	3.7 (3.4 to 4.1; p<0.001)
Pulse (per minute)	10.4 (27.8)	−0.9 (17.4)	−11.3 (−13.7 to −8.9; p<0.001)

*All changes in vital signs were calculated as the last minus the first measurement on scene.
RSI, rapid sequence intubation.

subgroup analysis comparing ischaemic versus haemorrhagic strokes

We compared the survival of patients that had received RSI to no-RSI separately for ischaemic and haemorrhagic strokes in the matched cohort. The survival for haemorrhagic stroke was OR 0.60 (95% CI: 0.41 to 0.90; p=0.01) and OR 0.66 (95% CI: 40 to 1.07; p=0.09) for ischaemic strokes (figure 2).

sensitivity analysis of unmeasured confounding and missing data

Two sensitivity analyses were completed. One accounted for the impact of missing covariate data; the other was a sensi- tivity analysis that quantified the effect of additional unmea- sured confounding. A sixth (12.5%) of the cohort had missing data on either a covariate or outcome (figure 1). Females had more missing outcomes and those with missing outcomes were younger. Missing outcomes had a lower initial respiratory rate and a lower initial systolic blood pressure. The year 2017 had the most missing survival data compared with 2009 with the least missing. For other covariates, no significant differences were found. We imputed missing covariate data and repeated the propensity matching and analysis, which found no obvious differences in survival estimates between the imputed and main analysis (figure 2).

We estimated the impact of unmeasured confounding for an additional 10% to 100% prevalence of an illness severity confounder in the RSI group and an extra 5% in the no-RSI group. Calculations were based on a relative risk of survival of 0.44 of this unmeasured confounder. Using a deterministic sensitivity analysis, our analysis showed that only when an extra 64% unaccounted illness severity in the RSI group is present then does survival difference become zero between RSI and the no-RSI groups (online supplementary figure S3). When an addi- tional unmeasured illness severity beyond 64% is reached in the RSI group, estimates start favouring RSI. The measure for illness severity used in this analysis is initial GCS, and it predicted survival well with an area under curve (AUC) of 0.78. When initial GCS is combined with the Walraven-Elixhauser comor- bidity score the AUC increases to 0.82.

limitations

If the anticipated effect of an intervention is small, then the use of observational methods to quantify the treatment effects has limitations. In such a case, any unmeasured confounding can obscure the true effect of the treatment under evaluation. We believe this is a significant limitation with our study, as the antic- ipated benefit of RSI is likely to be small. At best, our results can give indication of the direction of effect of RSI in stroke, not the exact survival estimate one might get from a randomised trial. Additionally, our data did not permit a comparison of good neurological survival, which would have been a more suitable outcome.

We selected the study cohort by identifying strokes from in-hospital records, but these records did not reliably indicate if each patient was transported by ambulance. To ascertain if a patient with stroke was transported by ambulance, we had to link the in-hospital records to out-of-hospital records. Therefore, it is possible that some strokes that were transported by ambulance could not be identified by such linkage. Consequently, we could not be certain that we included the exact proportion of strokes that were taken to hospital by ambulance. However, the propor- tion of stroke RSI very closely match numbers from previous reports from Victoria, Australia, suggesting that this study captured most (if not all) stokes with RSI.[3] Our analysis included only haemorrhagic or ischaemic strokes and not any unclassi- fiable strokes. Future research should investigate the effect of RSI on this subset of unclassifiable strokes. Also, the stroke diagnoses were based on ICD10-AM codes and were not adjudi- cated otherwise, which is less than ideal. We found differences in some covariates between those with missing survival outcomes. Although these differences reached statistical significance due to the large sample of this study, the magnitude of these differences was very small and probably clinically insignificant. Accordingly, the imputed analysis was not meaningfully different from the main analysis. We also estimate that the missing data is missing at random, based on our understanding of the data generation process, but cannot be sure of this.

It is also possible that the differences in results are due to unmeasured confounding. Unmeasured confounding due to illness severity was the main threat to the validity of our results, which could cause confounding by indication where sicker patients receive RSI, thus biassing estimates. Despite not having for-purpose illness severity scores such as NIHSS, we believe that no large unmeasured confounding is present in this study, as our measures of prognostic risk predicted survival well with an AUC of 0.82. If a prognostic risk measure has an AUC of more than 0.75, such an analysis is protected against confounding by illness and comorbidity risk.[16]

dIsCussIOn

This study showed lesser odds of survival for patients that received paramedic RSI for strokes in the out-of-hospital setting. We expected that sicker patients receive more RSI, causing confounding-by-indication. If there are more patients with a poor prognosis in the RSI group, then one might find lower survival than expected for RSI. Almost three-quarters of the RSI in this study were on haemorrhagic strokes, compared with the no-RSI group which was mostly ischaemic strokes. Since haem- orrhagic strokes had a poorer prognosis than ischaemic strokes, the large number of haemorrhagic strokes in the RSI group could bias results in favour of no-RSI. To counter this imbalance of prognosis between the RSI and no-RSI group, this analysis used propensity score matching. Ideally, a randomised controlled trial would be used to compare RSI to no-RSI, as this is the

most reliable method of ensuring that confounding factors are balanced between the treated and control groups. When a trial is not easily conducted, observational research using propensity score methods can be used. Propensity score matching attempt to emulate features of a randomised trial and can lessen measured confounding.[17]

While our analysis is likely the first out-of-hospital study to compare RSI to no-RSI for strokes, these results are not the first to point to possible harm from intubation in stroke. Observational in-hospital studies of haemorrhagic strokes and stroke thrombectomy showed decreased survival for those that received endotracheal intubation.[18 19] Numerous causes for the association of decreased survival and intubation have been proposed. Alterations of blood pressure after laryngoscopy and pre-medications, pneumonia, hypo/hyperoxia, hypo/hyperventilation, cardiac arrhythmias, adult respiratory distress syndrome and atelectasis as well as dysphagia associated with intubation are possible causes of decreased survival.[6 20–23] Some of these mechanisms were evident in our findings.

When scrutinising the minimum and final on-scene values of end-tidal CO_2, oxygen saturation and blood pressure, it is evident that a sizeable proportion of RSI had out-of range values. However, it must be said that these minimum (as compared with the final) values were not necessarily attributable to RSI; they were measured at any time on scene. We also found that pneumonia was significantly higher in the RSI group, but it is not possible to conclude that pneumonia was caused by RSI. When looking at the final measurements of on-scene oxygen saturation, carbon dioxide and blood pressure, it is clear that adverse events were below or similar to those of out-of hospital physicians.[24] Even so, these derangements associated with RSI as well as the increase in pneumonia could be factors that explain the decreased survival for RSI in this study. Future research should study the effects of vital-sign derangements in stroke.

Larynscopy might have transiently elevated blood pressure in some RSI. In a study by Perkins *et al*, laryngoscopy and intubation provoked a hypertensive response in 79% of their cohort,[22] and it could be that RSI provoked similar response in haemorrhagic strokes, for which the blood pressure was already elevated. While RSI can transiently elevate blood pressure, our analysis shows that the final on-scene systolic blood pressure tended to be *lower* than the initial blood pressure. The difference between the first and final blood pressure is 9.7 mm Hg lower for those that received RSI, compared with no-RSI. Stated differently, our analysis shows that RSI is associated with an almost 10 mm Hg larger decrease in systolic blood pressure when compared with no-RSI. Lowering blood pressure is a likely cause of decreased survival in stroke,[25] which might explain the decreased survival for strokes that received RSI in our analysis. Additionally, in the RSI group, a significant increase in pulse rate is apparent, compared with non-RSI, where the pulse rate decreased slightly. Although laryngoscopy in RSI could cause transient increase in blood pressure, we found a decrease when comparing the first to the final blood pressure. This apparent paradox indicates a complicated relationship between RSI and blood pressure that needs more clarification.

Generally, the intubation first-pass success and adverse event rate of paramedics in this study are on par with that of out-of-hospital physicians and better than other paramedic RSI studies.[24] Despite the proficiency in RSI by paramedics in Victoria, Australia, our observational analysis shows decreased survival for RSI in strokes. A randomised controlled trial is urgently needed.

COnClusIOns

This study shows decreased survival for patients that received paramedic initiated RSI for strokes, with haemorrhagic strokes having worse survival. Derangements in carbon dioxide levels, blood pressure, oxygen saturation and increased prevalence of pneumonia following RSI might explain the decreased survival for RSI. A clinical trial comparing RSI to no-RSI in stoke is needed.

Acknowledgements We are grateful to the staff at the Centre for Victorian Data Linkage as well as Salman Sabir at Ambulance Victoria for their assistance in obtaining the data for this study.

Contributors PFF conceived of the study, KS and PF collected data and PF analysed all data. All authors contributed to the manuscript. PF takes responsibility for the paper as a whole.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

ethics approval This study has received ethics approval. Monash University Human Research Ethics Committee gave ethics approval for this study (ref. no. 8618).

Provenance and peer review Not commissioned; externally peer reviewed.

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*See Appendix C3, Figures C3.1–C3.3 for the supplementary material

4.4 Principle findings and conclusions

This propensity score-matched cohort study of paramedic RSI is the first out-of-hospital study to show decreased survival for intubation in cases of stroke. The matched-cohort found 39% lesser odds of survival for RSI in strokes compared with a no-RSI sample. A subgroup analysis further showed no statistically significant survival difference for ischaemic strokes (odd ratio [OR] 0.66; 95% CI 0.40 to 1.07; $p = 0.09$) but survival odds for haemorrhagic cases were 40% lower for RSI OR 0.60 (95% CI 0.41 to 0.90; $p = 0.01$). This study is likely protected against bias problems that results from to unmeasured confounding and missing data. Additionally, a causal directed acyclic graph was compiled and broadly showed the effect of illness severity on survival estimates. Such a graph can be used to guide future research.[61] Researchers must acknowledge that any observational data on NTBP airway management have to properly account for illness severity.[1,2,62,63]

Overall, the propensity-matched study found a considerably larger decrease in systolic blood pressure for those that received RSI compared with no-RSI. Additional derangements in carbon dioxide (CO_2), oxygen, pulse rate and respiratory rate found here could, then, explain this decreased survival in stroke. Thus, one limitation of this study is its observational nature, and (despite rigorous analysis) one cannot rule out unmeasured confounding. Doctors Gibson, Jones and Watkins responded to this publication with a letter to the editor, to which the authors responded, please see Appendix C4.

Chapter 5: The Association of Blood-pressure Changes with Survival after Paramedic Rapid Sequence Intubation in Out-of-Hospital Stroke

5.1 Declaration for Chapter 5

5.1.1 Monash University

Fouche PF, Smith K.; Jennings P.A.; Bernard, S.; Boyle, M. The Association of Blood-pressure Changes with Survival after Paramedic Rapid Sequence Intubation in Out-of-Hospital Stroke. 2019.

5.1.2 Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work were the following:

Nature of contribution	Extent of contribution (%)
Lead author responsible for data collection, statistical analysis and manuscript preparation. Responsible author who accepts overall responsibility for publication.	90%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated.

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Paul Jennings	Manuscript preparation	–
Malcolm Boyle	Manuscript preparation	–
Karen Smith	Manuscript preparation, data collection	–
Stephen Bernard	Manuscript preparation	–

5.2 Background and context

Chapters 2 and 3 showed that RSI is common in the emergency setting, and is frequently used by paramedics in patients with stroke in Victroia, Australia.[2,3] Chapter 4 revealed that strokes which receive RSI by paramedics in Victoria have worse in-hospital survival, with heammorhagic strokes poorer survival compared to ischemic strokes.[1] Additionally, the propensity matched cohort study in chapter 4 compared systolic blood pressure changes during paramedic care for the RSI versus no-RSI group, and found that the RSI group had a much larger decrease in blood pressure. Specifically, the decrease in the RSI group was lower by almost 16 mmHg from the baseline, compared to the no-RSI group where the decrease was only 6mmHg.[1] In the mansucript of this matched study, the authors ventured that this decrease in systolic blood pressure could be a cause of poorer survival for RSI. Decreased blood pressure has been put forward as a mechanism that could cause worse survival after advanced airway managemnt.[1,3,64] Clearly, this blood pressure-related mechanism as a cause of poorer RSI survival in strokes warrants further investigation.

5.3 Aims of this chapter

Chapter 5 aims to test whether decreases in systolic blood pressure associated with paramedic RSI during the out-of-hospital phase is correlated with survival. This chapter presents a study that utilized a large data-linkage cohort of almost 44,000 strokes(wih 882 RSI) to investigate if a decrease, increase or static systolic blood pressure impacts survival to discharge. Firstly, a logistic regrsssion model is used to compare RSI survival for heammorhagic versus ischemic strokes. Secondly, this change in blood pressure continous variable was tested for its interaction with the stroke type to see if blood pressure changes impacts survival differenlty for heammorhagic versus ischemic strokes. If a decrease in systolic blood pressure is not associated with a survival difference, then the hypothesis that such blood pressure changes could impact RSI survival carries less weight.

The Association of Blood-pressure Changes with Survival after Paramedic Rapid Sequence Intubation in Out-of-Hospital Stroke

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Key terms: Rapid sequence intubation; paramedic; stroke; interactions

Word count: 2,179

Author contributions: PF conceived of the study, KS and PF collected data and PF analysed all data. All authors contributed to the manuscript. PF takes responsibility for the paper as a whole.

Abstract

Background

Rapid sequence intubation (RSI) is used to secure the airway of some strokes. Recent observational studies suggest that RSI is associated with poorer survival, and that decreases in systolic blood pressure following RSI could be a cause of worse survival. This study aims to find if decreased systolic blood pressure after paramedic RSI is associated with poorer survival in strokes transported by ambulance.

Methods

This study was a retrospective analysis of all haemorrhagic and ischemic stroke patients that received paramedic RSI attended by Ambulance Victoria, Australia. Logistic regression predicted the survival for strokes that had received RSI. The change in systolic blood pressure during paramedic care was the main predictor.

Results

Of 43,831 strokes 882 (2%) received RSI. Almost 48% of RSI had a decline in systolic blood pressure of more than 20% from baseline, and the decline in systolic blood pressure after RSI was larger for haemorrhagic compared to ischemic strokes; -21.3 versus -10.9 mmHg; difference 10.4 mmHg (95% CI -16.5 to -4.3,$p<0.001$). Sixteen percent of the RSI group had an episode of hypotension anytime during the out-of-hospital care. For each 10mmHg increase in systolic blood pressure with RSI for haemorrhagic strokes a decrease of 14% in the odds of survival is apparent ($p= 0.002$), and for ischemic strokes an increase 8% in the odds of survival was found ($p= 0.24$).

Conclusions

Paramedic RSI- related decrease in systolic blood pressure is not associated with a significantly decreased survival, and this lack of association concords with stroke anaesthesia trials.

Introduction

Strokes account for 10% of deaths worldwide.[1] Rapid Sequence intubation (RSI) is used in the emergency setting to protect the airway in strokes, with perhaps 6% to 79% of strokes receiving intubation, depending on the stroke type.[2] Rapid sequence intubation is used to secure the airway using sedative and paralytic drugs to facilitate endotracheal intubation.[2] Strokes form 37% of RSI undertaken by paramedics in Victoria, Australia.[3] Despite the not-infrequent use of RSI in unconscious out-of-hospital strokes, no high quality evidence exists to support the use of RSI for strokes.[2-4] However, a recent propensity- matched cohort study of paramedic RSI found decreased odds of survival for RSI in both haemorrhagic and ischemic strokes.[4] That study speculated that decreases in blood pressure with RSI might explain the decreased survival in stroke. Specifically, the authors found an almost 10 mmHg larger decrease in systolic blood pressure in the RSI group of the matched cohort, and speculated that this decrease could be the cause of decreased survival for RSI. This analysis aims to test if RSI-related decrease in systolic blood pressure is associated with poorer survival in strokes transported by ambulance.

Methods

Study setting and data sources

Victoria has 6.5 million residents serviced by a two-tier emergency medical service. During the study period Mobile Intensive Care Paramedics were authorized to provide RSI to patients that have a Glasgow Coma Scale of less than 10 using suxamethonium as the primary paralytic, with pancuronium used to maintain paralysis.[5] Midazolam, morphine/midazolam infusions, atropine, ketamine and fentanyl were available to aid RSI.[5] This study analysed data from 131 hospitals and clinics in Victoria, Australia for the ten year period 1 January 2008 to 31 December 2017. The characteristics of this dataset have been described previously.[4] Monash University Human Research Ethics Committee provided ethics approval (ref. no. 8618).

Selection of cohort

This study included all patients of any age that were treated and transported by Ambulance Victoria and had received paramedic RSI with a hospital diagnosis of stroke. We excluded transient ischemic attack and strokes that could not be classified as either haemorrhagic or ischemic. Instances of stroke were identified by the Australian modification of ICD10 codes: I60, I61, I62.9 and I63. We initially selected all hospital records of patients with stroke codes, irrespective of ambulance transportation. These stroke in-hospital records were then linked to the Ambulance Victoria out-of-hospital records to select those that had a stroke and were transported by ambulance.[4]

Predictors and outcomes

The primary outcome was survival to hospital discharge. Potential predictors include demographic, treatment, baseline observations ("vital signs") and scene/transport time intervals. Illness severity and comorbidity are important confounders in strokes, and we adjusted for illness severity using Glasgow Coma Scale. Whilst Glasgow Coma Scale was not specifically designed as a severity score for strokes, it could be similarly predictive of in-hospital survival as National Institutes of Health Stroke Scale.[6] We adjusted for comorbidity by calculating the Walraven-Elixhauser comorbidity score.[7] No adjustment for any in-hospital interventions were done to avoid conditioning on a mediator variable.[8] Changes in systolic blood pressure during paramedic care were calculated by subtracting the first systolic blood pressure upon scene arrival from the last values before handover at the emergency department.[4] Change in systolic blood pressure can have positive, negative or no-change values depending on whether blood pressure decreased, increased or stayed the same during the prehospital phase. Change in systolic blood pressure was analysed as a continuous variable.

Definitions

Strokes are defined by ICD10-AM codes and subtyped for ischemic and haemorrhagic strokes. Rapid sequence intubation is defined as the attempted or successful placement of an endotracheal tube in the trachea after receiving a paralytic agent. Successful placement of endotracheal tube in the trachea was confirmed using clinical means and end-tidal CO_2 waveform. Hypotension was defined as a systolic blood

pressure less than 90 mmHg.[9] We also enumerated cases with a decline in systolic blood pressure of more than 20% from baseline.

Statistical analysis

Stata version 14 (Stata Corp, College Station, Texas, USA) was used to analyse data. Categorical variables are presented as frequencies, and continuous variables as means with standard deviations. Hypothesis tests were two-sided, with a significance level of $p < 0.05$.

Model building and main analysis

We utilized a maximum likelihood-fitted logistic regression model on complete observations that had received RSI. Variables were included in the final model if they were potential confounders of the relationship between blood pressure changes and survival in the RSI group. A causal directed acyclic graph published recently showed that it is critical to adjust for age, comorbidities, illness severity, sex, initial systolic blood pressure and initial oxygen saturation.[4] Therefore, these confounding variables were adjusted for regardless of their statistical significance. Non-linear main-effect terms were fitted using fractional polynomials if appropriate. Goodness of fit was tested using the Hosmer and Lemeshow test.[10] The regression model was assembled on all non-missing observations. Previous work using this same dataset showed that missingness were clinically insignificant and did not meaningfully impact estimates.[4] As such, no sensitivity analyses for the impact of missing data were conducted.

Interaction

This analysis also tested how changes in systolic blood pressure interact with haemorrhagic versus ischemic stroke in this RSI-only group. The interaction was analysed as a continuous variable and displayed graphically. Any such interaction in the RSI-only group might indicate that RSI-related systolic blood pressure changes influences survival differently for ischemic versus haemorrhagic strokes. An interaction term that was significant at a five percent level was considered as evidence of statistical interaction.

Results

Of 43,831 strokes 882 (2%) received RSI (Figure 1). A total of 773(88%) RSI had complete data and baseline characteristics are compared in Table 1. Almost 69% of all RSI in this cohort were conducted in haemorrhagic strokes, and haemorrhagic strokes were younger and more likely to be female compared to ischemic strokes (Table1).

Change in systolic blood pressure

The mean change in systolic blood pressure in the out-of-hospital phase for all 773 strokes that received RSI was -18.3 mmHg (SD=41.8 mmHg). Sixteen percent of the RSI group had an episode of hypotension anytime during the out-of-hospital care, and 47.6% of RSI had a decline in systolic blood pressure of more than 20% from baseline (Table 2). The mean decline in systolic blood pressure after RSI is larger for haemorrhagic compared to ischemic strokes -21.3 versus -10.9 mmHg; difference 10.4 mmHg(95% CI -16.5 to -4.3,$p<0.001$).

Despite the decrease in systolic blood pressure associated with RSI, our adjusted logistic regression analysis indicates that this decrease was not associated with poorer survival for neither haemorrhagic nor ischemic stroke (Figure 2). This adjusted regression analysis shows that for each 10mmHg increase in systolic blood pressure for haemorrhagic strokes a decrease of 14% in the odds of survival is apparent (p= 0.002). In contrast, for each 10mmHg increase in systolic blood pressure for ischemic strokes an increase 8% in the odds of survival was found (p= 0.24). The interaction of stroke type and change in systolic blood pressure was significant (p=0.04) (Figure 2). This model had good fit; Hosmer-Lemeshow chi^2 (DF=8) = 12.8, p=0.12.

Limitations

The utility of observational methods to reveal treatment effects are limited, especially if the anticipated effect is small.[11] Additionally, we could not compare good neurological survival, which would have been a more suitable. Our data did not allow for a minute-by-minute comparison of blood pressure changes during the RSI peri-intubation period. In this analysis we calculated the change in blood pressure by subtracting the first values upon scene arrival from the last values during paramedic care, similar to recent analysis.[4,12]

Typically, a paramedic measures a blood pressure upon arrival at the patient side, and finally before handover to the emergency department. We believe that comparing the first systolic blood pressure measured upon arrival to the last (measured after all prehospital treatments were given) would show the impact of the effects of RSI on blood pressure (after adjustment for confounders). In a previous analysis of this stroke dataset sizable differences were found between the RSI group and a matched non-RSI group.[4] As such, the change between the first and the last blood pressure are worthwhile comparing despite these changes not being as fine-grained as would be ideal.

It is also likely that these results might still be somewhat biased due to unmeasured confounding. However, our measures of prognostic risk due to illness severity and comorbidities together predicted survival well with an area under curve of 0.83, which is higher than the 0.75 that would provide evidence of adequate risk adjustment.[13]

Discussion

This analysis shows that paramedic RSI in stroke patients is associated with a decrease in systolic blood pressure during paramedic care, and that these decreases were not associated with a significant decrease in survival for either stroke type. This surprising finding is mirrored in the results of the three recent randomized trials that compared conscious sedation to general anaesthesia in ischemic stroke thrombectomy.[14-17] A meta-analysis by Schönenberger et al of these three trials showed a decline in systolic blood pressure of more than 20% was much more frequent in the general anaesthesia group than the procedural sedation group (80.8% vs 53.1%).[14] Similar to the Schönenberger meta-analysis, we found sizable decreases in systolic blood pressure in this prehospital anaesthesia (RSI) cohort and that this larger decrease in blood pressure was not associated with worse survival.

Although our results of no-decrease in survival after a drop in systolic blood pressure out-of-hospital RSI have commonalities with the three in-hospital trials, it must be stated that there are important differences between these trials and our study. For example, in our cohort RSI was done by paramedics and in the out-of-hospital setting. There are other essential differences between the trials and our cohort, but we do believe that there are enough similarities that a comparison is warranted. Both these trials and our cohort

employed anaesthesia in strokes and was compared to no-anaesthesia, and both found more instances of decreased blood pressure in the anaesthesia group. Both the trials and our study found that the decrease in systolic blood pressure was not a likely cause of poorer survival.

The interaction of stroke type and a change in systolic blood pressure was statistically significant. Therefore, this analysis provides evidence that a change in systolic blood pressure after RSI impacts survival differently when comparing haemorrhagic to ischemic stroke. Such an interaction implies that RSI-related blood pressure changes could impact survival differently between the two stroke types and that RSI itself has a different effect on the two stroke kinds.

Our finding that decreased blood pressure does not correlate with poorer survival in stroke is surprising, since RSI- blood pressure changes are thought a likely cause of poorer survival.[3,4,9,18] However, there is evidence that blood pressure lowering is safe and might be beneficial in patients with intra-cerebral heammorhage, and that blood pressure lowering in patients with ischemic stroke might not cause worse survival.[19] Further research that cast light on the mechanisms that underlie the apparent poorer survival for paramedic RSI in strokes is therefore needed. There is no high quality research to support RSI for any non-traumatic brain pathology, either in the emergency department out of hospital setting.[2] Therefore, a randomized controlled trial in stroke RSI is essential to support practice.[2,4]

Conclusions

Paramedic rapid sequence intubation related decreases in systolic blood pressure is not associated with decreased survival, and this lack of association concords with stroke anaesthesia trials. A stroke trial comparing RSI to no-RSI in the out-of-hospital setting is urgently needed.

Acknowledgements

We are grateful to the staff at the Centre for Victorian Data Linkage as well as Salman Sabir at Ambulance Victoria for their assistance in obtaining the data for this study.

Ethics approval statements

This study has received ethics approval. Monash University Human Research Ethics Committee gave ethics approval for this study (ref. no. 8618).

Clinical Trial Registration

Not applicable

Funding statement

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests

None declared

Figure 1 Patient selection for a cohort of RSI with stroke transported by Ambulance

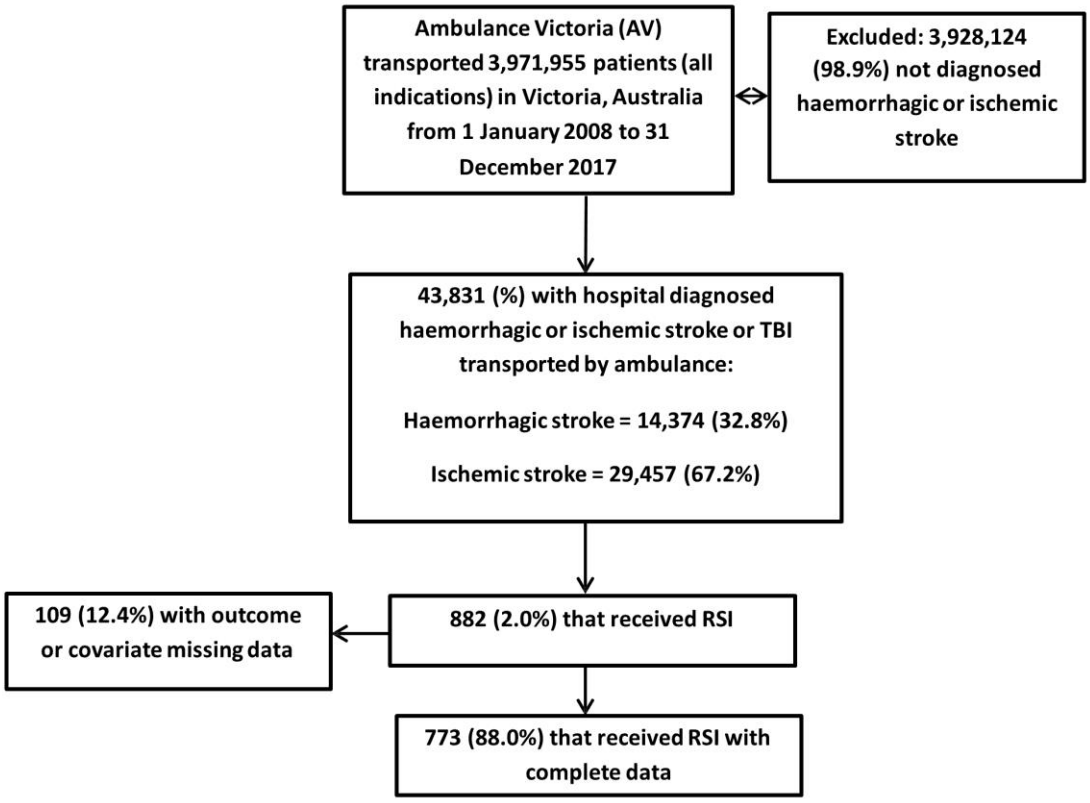

Figure 2 Survival associated with changes in systolic blood pressure in a cohort of 773 strokes that received RSI by paramedics

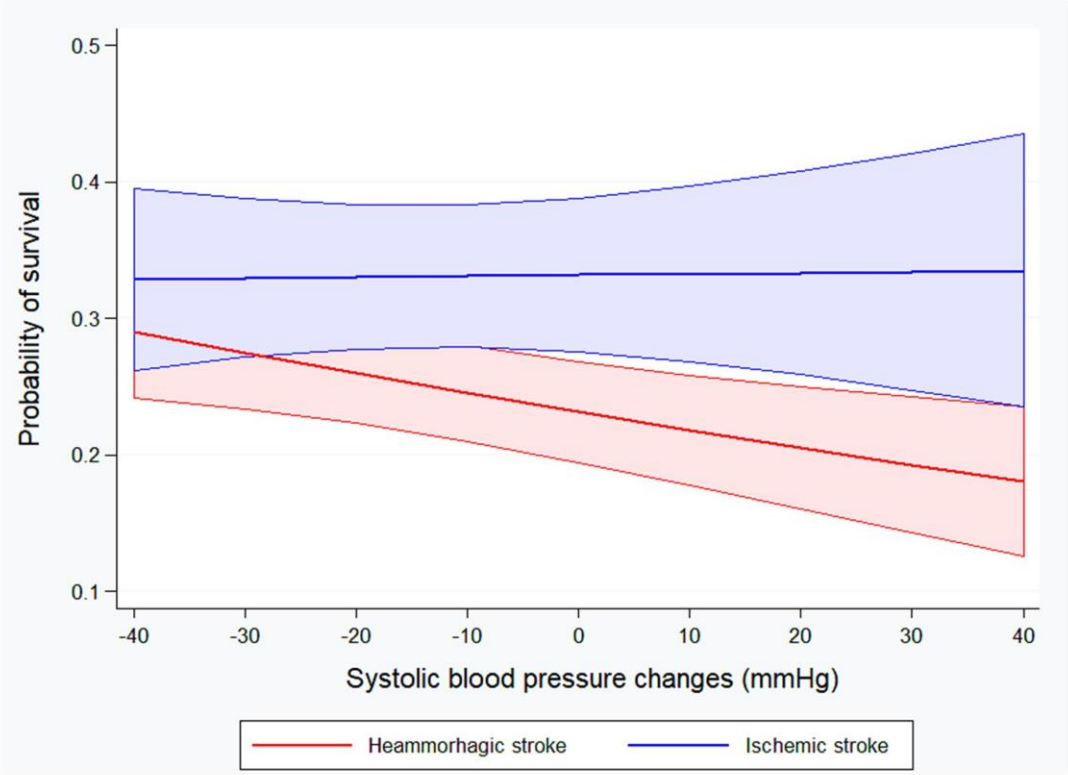

Table 1 Patient, demographic, prognostic and in-hospital factors in in a cohort of 773 strokes that received paramedic RSI

	Patients, No. (%)		
Characteristic	**Total (N = 773)**	**Haemorrhagic stroke (n = 531)**	**Ischemic stroke (n =242)**
Demographic			
Age, mean (SD), years	65.3(15.6)	64.6(16.1)	66.8(14.6)
Sex			
Male	380(49.2)	246(46.3)	134(55.4)
Female	393(50.8)	285(53.7)	108(44.6)
Illness severity/comorbidity, mean(SD)			
Elixhauser comorbidity score *	18.1(7.4)	16.4(6.3)	22.0(8.0)
Initial Glasgow Coma Scale	6.1(3.3)	6.0(3.4)	6.2(3.1)
Observations, mean (SD)			
Initial pulse rate	88.2(27.8)	86.5(26.7)	92.1(29.7)
Final pulse rate	99.1(22.6)	99.6(21.2)	97.9(25.5)
Initial systolic blood pressure	162.6(44.4)	170.3(44.2)	145.8(40.0)
Final systolic blood pressure	145.4(32.0)	150.0(33.2)	135.1(26.5)
Initial respiratory rate	17.8(7.9)	17.6(7.8)	18.3(8.1)
Final respiratory rate	12.0(7.3)	12.1(7.3)	11.9(7.2)
Initial SPO_2	93.6(10.5)	94.4(8.6)	91.7(13.7)
Final SPO_2	98.4(4.6)	98.3(5.1)	98.5(3.3)
Derangements in systolic blood pressure			
Decline in blood pressure > 20%	368(47.6)	262(49.3)	106(43.8)
Blood pressure <90 mmHg at any time	124(16.0)	78(14.7)	46(19.0)
Ambulance time intervals, minutes mean (SD)			
Response time	15.8(16.6)	15.0(14.5)	17.6(20.4)
Scene time	58.0(25.3)	56.7(25.8)	58.6(25.1)
Transport time	29.7(22.4)	29.2(21.2)	30.8(24.8)
Hospital			
Time in intensive care unit, mean (SD), hours	111.2(137.6)	97.0(127.2)	135.6(151.1)
Mechanical ventilation in intensive care unit, mean (SD), hours	82.1(112.7)	73.6(104.1)	96.7(125.3)
Hospital length of stay, mean (SD), days	10.1(20.4)	8.2(18.5)	14.3(23.6)
Emergency department length of stay mean (SD), minutes	314.6(235.3)	317.3(228.6)	305.4(257.5)
Year			
2008	82(10.6)	56(10.6)	26(10.7)
2009	80(10.4)	54(10.2)	26(10.7)
2010	103(13.3)	72(13.6)	31(12.8)
2011	94(12.2)	62(11.7)	32(13.2)
2012	81(10.5)	57(10.70	24(9.9)
2013	69(8.9)	45(8.5)	24(9.9)
2014	52(6.7)	34(6.4)	18(7.4)
2015	55(7.1)	37(7.0)	18(7.4)
2016	80(10.4)	60(11.3)	20(8.3)
2017	77(10.0)	54(10.2)	23(9.5)

* Scaled to avoid negative values

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5.4. Principle findings and conclusions

This analysis measured the association of changes of systolic blood pressure in the RSI group of a large data-linkage cohort. Almost 48% of RSI had a decline in systolic blood pressure of more than 20% from baseline, and the decline in systolic blood pressure after RSI was larger for haemorrhagic compared to ischemic strokes; -21.3 versus -10.9 mmHg. Despite the decrease in systolic blood pressure in this RSI group, the decrease was not associated with poorer survival for either haemorrhagic nor ischemic strokes. Stroke type and the change in systolic blood pressure interacted significantly, implying that changes in blood pressure after RSI impacts survival differently for the two types of stroke. Paramedic rapid sequence intubation related changes in systolic blood pressure is not associated with decreased survival, and this lack of association concords with stroke anaesthesia trials. Consequently, a stroke RCT comparing RSI to no-RSI in the out-of-hospital setting is urgently needed.

Chapter 6: Utility of the brain trauma evidence to inform paramedic RSI in out-of-hospital stroke

6.1 Declaration for Chapter 6

6.1.1 Monash University

Fouche, P.F., Jennings, P.A., Boyle, M. *et al.* The utility of the brain trauma evidence to inform paramedic rapid sequence intubation in out-of-hospital stroke. *BMC Emerg Med* 20, 5 (2020). Available from: https://doi.org/10.1186/s12873-020-0303-9

6.1.2 Declaration by candidate

In the case of Chapter 6, the nature and extent of my contribution to the work were the following:

Nature of contribution	Extent of contribution (%)
Lead author responsible for data collection, statistical analysis and manuscript preparation. Responsible author who accepts overall responsibility for publication.	90%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated.

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Paul Jennings	Manuscript preparation	–
Malcolm Boyle	Manuscript preparation	–
Karen Smith	Manuscript preparation, data collection	–
Stephen Bernard	Manuscript preparation	–

6.2 Background and context

Chapters 2 and 3 demonstrated that RSI is commonly used in emergency settings and that NTBPs such as stroke form a large part of paramedic intubation.[2,3] Stroke is also the most common pathology that receives RSI, and has the largest mortality rate among recipients.[3] Thereafter, Chapter 4 found that stroke recipients of paramedic RSI have worse survival-to-hospital discharge, especially if haemorrhagic in nature. These observational studies do have limitations, with one being a tendency to show only confounded associations rather than causality.[56] Even so, the Chapter 4 study show that paramedic RSI *is* associated with decreased survival in cases of stroke. Ultimately, the best evidence to support RSI to date resides in the Bernard et al. RSI in TBI trial.[39]

Fitzgerald et al. have pointed to potential shortcomings in Bernard's RCT, such as over-reliance on secondary outcomes and failure to account for multiple outcomes (see Section 1.1.5).[65] Here, the non-significant *p*-values and large CIs for outcomes such as survival to discharge in the Bernard et al. trial imply a lack of statistical power. This deficit and the limitations pointed out in Fitzgerald et al. indicate that the research might not be considered as solid evidence to support RSI for any indication, including TBI and strokes. If the Bernard trial were sufficiently powered, and if the inadequacies pointed out by Fitzgerald were rectified, could the findings be applied to cases of stroke? That is, are strokes and TBI similar enough that the TBI evidence can be translated to strokes and other NTBPs? This begs the question; does RSI in TBI affect survival similarly for stroke?

6.3 Aims of this chapter

Chapter 6 aims to investigate whether researchers can transfer the TBI RSI evidence to strokes by studying how RSI affects brain injury compared with stroke in terms of survival. The RSI procedure itself is comprised of many factors, including whether intubation is successful and how many attempts success necessitates. RSI further consists of the administration of all the intubation and anaesthesia related medications, such as paralytics and sedatives and/or hypnotics. Furthermore, RSI is also related to scene time due to the time it takes to RSI. Rapid sequence intubation could have a direct effect on "vital signs" such as blood pressure, pulse, GCS, $ETCO_2$, SPO_2 and so forth. Each of these components might

affect survival differently for TBI and stroke, and have the capacity to produce differences in outcome between both pathologies.

This chapter employs a large data-linkage cohort to investigate how these components of RSI (and therefore RSI itself) impact survival differently for TBI compared to ischemic and haemorrhagic strokes. We utilized a dataset in excess of 107,000 patient encounters, obtained after deterministic linkage of hospital and in hospital records. The governance and ethics applications, plus liaison with the data custodians and linkage of the datasets was very time consuming, and took a year-and-a-half. The statistical analysis itself took six months. To show the lack of transferability of the brain trauma evidence of RSI to stroke, we tested for statistical interactions in the RSI cohort. All the RSI components were tested for interactions separately, and if any of these interactions were significant at a 5% level, then it might follow that RSI impacts survival differently when TBI is compared to strokes. Such differential impacts of RSI components on survival would imply that the brain trauma evidence cannot be transferred to stroke RSI.

Fouche et al. BMC Emergency Medicine (2020) 20:5
https://doi.org/10.1186/s12873-020-0303-9

BMC Emergency Medicine

RESEARCH ARTICLE Open Access

The utility of the brain trauma evidence to inform paramedic rapid sequence intubation in out-of-hospital stroke

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Abstract

Background: Rapid sequence intubation (RSI) is used to secure the airway of stroke patients. Randomized controlled trial evidence exists to support the use of paramedic RSI for traumatic brain injury (TBI), but cannot necessarily be applied to stroke RSI because of differences between the stroke and TBI patient. To understand if the TBI evidence can be used for stroke RSI, we analysed a retrospective cohort of TBI and strokes to compare how survival is impacted differently by RSI when comparing strokes and TBI.

Methods: This study was a retrospective analysis of 10 years of in-hospital and out-of-hospital data for all stroke and TBI patients attended by Ambulance Victoria, Australia. Logistic regression predicted the survival for ischemic and haemorrhagic strokes as well as TBI. The constituents of RSI, such a medications, intubation success and time intervals were analysed against survival using interactions to asses if RSI impacts survival differently for strokes compared to TBI.

Results: This analysis found significant interactions in the RSI-only group for age, number of intubation attempts, atropine, fentanyl, pulse rate and perhaps scene time and time- to-RSI. Such interactions imply that RSI impact survival differently for TBI versus strokes. Additionally, no significant difference in survival for TBI was found, with a − 0.7% lesser survival for RSI compared to no-RSI; OR 0.86 (95% CI 0.67 to 1.11; p = 0.25). Survival for haemorrhagic stroke was − 14.1% less for RSI versus no-RSI; OR 0.44 (95% CI 0.33 to 0.58; p = 0.01) and was − 4.3%; OR 0.67 (95% CI 0.49 to 0.91; p = 0.01) lesser for ischemic strokes.

Conclusions: Rapid sequence intubation and related factors interact with stroke and TBI, which suggests that RSI effects stroke survival in a different way from TBI. If RSI impact survival differently for strokes compared to TBI, then perhaps the TBI evidence cannot be used for stroke RSI.

Keywords: Traumatic brain injury, Stroke, rapid sequence intubation, Paramedic

Background

Strokes account for 10% of deaths worldwide [1]. Rapid Sequence intubation (RSI) is used in the emergency setting to improve survival in strokes, with perhaps 6 to 79% of strokes receiving intubation, depending on the stroke type [2]. Rapid sequence intubation is used to secure the airway using sedative and paralytic drugs to facilitate endotracheal intubation [2]. Strokes form 37% of RSI for non-traumatic brain pathologies undertaken by paramedics in Victoria, Australia [3]. Despite the not-infrequent use of RSI in unconscious out-of-hospital acquired brain injuries, no high quality evidence exists to support the use of RSI for strokes [2–4]. A randomized controlled trial of RSI in traumatic brain injury (TBI) exist [5], but the evidence from this trial cannot necessarily be applied to stroke RSI due to differences between the stroke and TBI patient [2–4].

Lower RSI survival for strokes compared to TBI suggests that the evidence from TBI might not be applicable to RSI in stroke [4]. It is important to investigate if brain trauma RSI evidence is transferable to strokes. That is, it would be vital to understand the RSI components that

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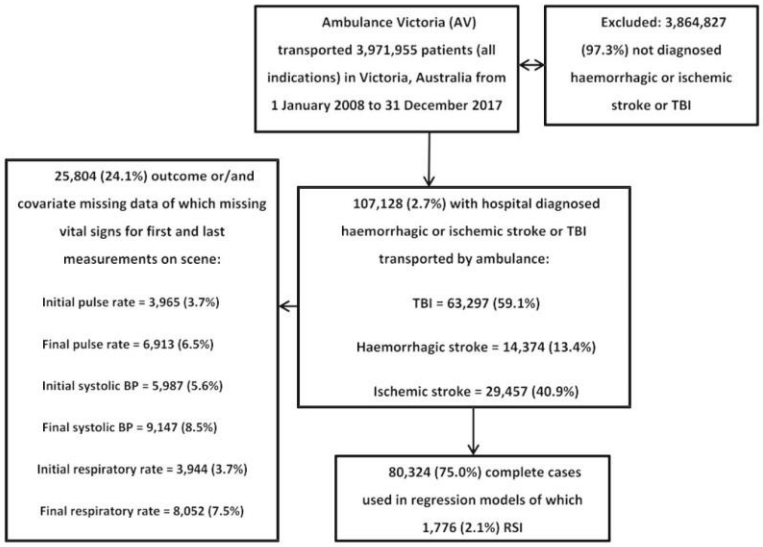

Fig. 1 Patient selection for a cohort of RSIin stroke and TBI

cause the survival difference of TBI compared to strokes. This study aims to find the constituents of RSI that could cause different survival between TBI and strokes. If any component of RSI impacts survival differently for TBI compared to strokes, it would follow that RSI itself has a different effect on these two pathologies. If RSI causes dissimilar survival for these two illnesses, then this would mean that the RSI TBI evidence-base cannot be transferred to strokes. Any such differences would imply that a stroke RSI trial is needed.

Methods

Study setting and data sources

Victoria has 6.3 million residents serviced by a two-tier emergency medical service. Mobile Intensive Care Paramedics are authorized to provide RSI to patients that have a Glasgow Coma Scale of less than 10 using suxamethonium as the primary paralytic, with pancuronium used to maintain paralysis [6]. Midazolam, morphine/midazolam infusions, atropine, ketamine and fentanyl were available to aid RSI [6]. This study analysed data from 131 hospitals and clinics in Victoria, Australia for the 10 year period 1 January 2008 to 31 December 2017. Monash University Human Research Ethics Committee provided ethics approval (ref. no. 8618).

Selection of cohort

This study included all patients of any age that were treated and transported by Ambulance Victoria, with a hospital diagnosis of TBI or stroke. We excluded transient ischemic attack and strokes that could not be classified as either haemorrhagic or ischemic. Instances of stroke and TBI were identified by the Australian modification of ICD10 codes: S06 (Intracranial injury), I60 (subarachnoid haemorrhage), I61 (intracerebral haemorrhage), I62.9 (intracranial haemorrhage [non-traumatic], unspecified) and I63 (cerebral infarction). We initially selected all hospital records of patients with TBI and stroke codes, irrespective of ambulance transportation. These TBI and stroke in-hospital records were then linked to the Ambulance Victoria out-of-hospital records to select those that had a stroke or TBI and were transported by ambulance [4].

Predictors and outcomes

The primary outcome was survival to hospital discharge. Potential predictors include demographic, treatment, baseline observations ("vital signs") and scene/transport time intervals. Illness severity and comorbidity are important confounders in strokes and TBI, and we adjusted for illness severity using Glasgow Coma Scale. Whilst Glasgow Coma Scale was not specifically designed as a severity score for TBI and strokes, it could be similarly predictive of in-hospital survival as NIHSS for strokes [7], and has strong prognostic value in TBI [8]. We adjusted for comorbidity by calculating the Walraven-Elixhauser comorbidity score [9]. No adjustment for any in-hospital interventions were done to avoid conditioning on a mediator variable [10].

Table 1 Patient, demographic, prognostic and in-hospital factors in in a cohort of 80,324 strokes and traumatic brain injury

Characteristic	Patients, No. (%)		
	Total (*n* = 80,324)	RSI(*n* = 1776)	No-RSI (*n* = 78,548)
Demographic			
Age, mean (SD), years	61.6 (22.5)	52.2 (22.5)	61.8 (24.2)
Sex			
Male	46,726 (58.1)	1125 (63.3)	45,601 (58.1)
Female	33,598 (41.8)	651 (36.7)	32,947 (41.6)
Illness			
Haemorrhagic stroke	11,133 (13.9)	531 (29.9)	10,602 (13.5)
Ischemic stroke	26,754 (33.3)	242 (13.6)	26,512 (33.8)
Traumatic brain injury	42,437 (52.9)	1003 (56.5)	41,434 (52.8)
Illness severity/comorbidity, mean (SD)			
Elixhauser comorbidity score[a]	17.2 (7.0)	17.3 (6.6)	17.2 (7.0)
Initial Glasgow Coma Scale	13.5 (2.8)	6.4 (3.6)	13.7 (2.5)
Observations, mean (SD)			
Initial pulse rate	85.4 (19.5)	92.9 (28.8)	85.2 (19.2)
Final pulse rate	82.6 (18.0)	101.5 (22.4)	82.1 (17.6)
Initial systolic blood pressure	140.6 (31.5)	145.7 (41.8)	140.5 (31.2)
Final systolic blood pressure	139.3 (28.5)	136.4 (29.7)	139.3 (28.5)
Initial respiratory rate	17.7 (4.6)	18.3 (8.0)	17.7 (4.5)
Final respiratory rate	16.9 (4.0)	12.2 (7.5)	17.0 (3.8)
Initial SPO_2	96.1 (5.1)	94.1 (9.6)	96.1 (4.9)
Final SPO_2	97.2 (3.4)	98.5 (4.6)	97.2 (3.3)
Ambulance time intervals, minutes mean (SD)			
Response time	21.1 (23.1)	19.2 (18.9)	21.2 (23.2)
Scene time	24.3 (99.9)	60.7 (35.0)	23.4 (100.7)
Transport time	25.6 (21.0)	31.5 (23.5)	25.5 (20.9)
Hospital			
Time in intensive care unit, mean (SD), hours	125.2 (161.3)	156.9 (172.2)	119.4 (158.5)
Mechanical ventilation in intensive care unit, mean (SD), hours	106.8 (148.9)	117.9 (144.6)	103.8 (150.0)
Hospital length of stay, mean (SD), days	6.8 (10.2)	13.3 (20.5)	6.6 (9.8)
Emergency department length of stay mean (SD), minutes	426.1 (318.7)	272.2 (214.8)	430.2 (320.0)
Year			
2008	6497 (8.1)	148 (8.3)	6349 (8.1)
2009	7435 (9.3)	142 (8.0)	7293 (9.3)
2010	7834 (9.8)	167 (9.4)	7667 (9.8)
2011	8614 (10.7)	215 (12.1)	8399 (10.7)
2012	8293 (10.3)	205 (11.5)	8088 (10.3)
2013	7962 (9.9)	194 (10.9)	7768 (9.9)
2014	6416 (8.0)	123 (6.9)	6293 (8.0)
2015	8581 (10.7)	164 (9.2)	8417 (10.7)
2016	9101 (11.3)	221 (12.4)	8880 (11.3)
2017	9591 (11.9)	197 (11.1)	9394 (12.0)

[a]Scaled to avoid negative values

Table 2 Comparison of changes in vital signs in a cohort of 80,324 strokes and traumatic brain injury

Change in vital sign[a]	RSI (mean; 95% CI)	No-RSI (mean; 95% CI)	Difference (95% CI; P)
Haemorrhagic strokes			
Systolic blood pressure (mmHg)	−15.8 (−17.8 to −13.9)	−2.0 (−2.4 to −1.6)	−13.8 (− 15.8 to − 11.8; $p < 0.001$)
SPO_2(%)	2.0 (1.4 to 2.5)	1.8 (1.7 to 2.0)	0.1 (−0.5 to 0.7; $p = 0.72$)
Respiratory rate (per minute)	−5.8 (−6.1 to −5.5)	−0.4 (− 0.5 to − 0.4)	−5.4 (− 6.1 to − 5.5; $p < 0.001$)
Glasgow Coma Scale (unit)	−3.5 (−3.6 to −3.3)	− 0.08(− 0.1 to − 0.04)	−3.4 (− 3.5 to − 3.2; $p < 0.001$)
Pulse (per minute)	13.2 (11.9 to 14.3)	−1.7 (− 1.9 to − 1.4)	14.8 (13.6 to 16.1; $p < 0.001$)
Ischemic strokes			
Systolic blood pressure (mmHg)	−9.8 (− 12.1 to − 1.1)	−1.3 (− 1.5 to − 1.1)	−8.5 (− 10.8 to − 6.2; $p < 0.001$)
SPO_2(%)	4.2 (3.6 to 4.8)	1.2 (1.1 to 1.3)	3.0 (2.3 to 3.6; $p < 0.001$)
Respiratory rate (per minute)	−6.8 (−7.1 to − 6.5)	−0.5 (− 0.48 to − 0.43)	− 6.4 (− 6.7 to − 6.1; $p < 0.001$)
Glasgow Coma Scale (unit)	−3.9 (− 4.1 to − 3.8)	0.1 (0.1 to 0.14)	− 4.0 (− 4.2 to − 3.9; $p < 0.001$)
Pulse (per minute)	4.7 (3.3 to 6.0)	−1.5 (− 1.6 to − 1.4)	6.2 (4.8 to 7.6; $p < 0.001$)
Traumatic brain injuries			
Systolic blood pressure (mmHg)	−2.6 (− 3.6 to − 1.5)	−1.3 (− 1.4 to − 1.1)	−1.3 (− 2.4 to − 0.2; $p = 0.02$)
SPO_2(%)	2.2 (1.8 to 2.5)	1.0 (0.9 to 1.1)	1.2 (0.8 to 1.5; $p < 0.001$)
Respiratory rate (per minute)	−6.1 (− 6.3 to − 5.9)	−0.9 (− 0.9 to − 0.85)	− 5.2 (− 5.4 to − 5.0; $p < 0.001$)
Glasgow Coma Scale (unit)	−5.6 (− 5.7 to − 5.5)	0.3 (0.2 to 0.3)	−5.8 (− 5.9 to − 5.7; $p < 0.001$)
Pulse (per minute)	7.4 (6.6 to 8.2)	−4.5 (− 4.6 to − 4.4)	11.9 (11.0 to 12.7; $p < 0.001$)

[a]All changes in vital signs calculated as the last minus the first measurement on scene. Means are adjusted for age, initial GCS, year, initial respiratory rate, initial pulse rate, initial systolic blood pressure and Elixhauser comorbidity score

Definitions

Strokes and TBI are defined by ICD10-AM codes and subtyped for ischemic and haemorrhagic strokes as well as TBI. Rapid sequence intubation is defined as the attempted or successful placement of an endotracheal tube in the trachea after receiving a paralytic agent. Successful placement of endotracheal tube in the trachea was confirmed using clinical means and end-tidal CO_2 waveform.

Statistical analysis

Stata version 14 (Stata Corp, College Station, Texas, USA) was used to analyse data. Categorical variables are presented as frequencies, and continuous variables as means with standard deviations. Categorical variables were compared with the χ^2 test and continuous predictors with the t-test or Wilcoxon rank-sum test. Hypothesis tests were two-sided, with a significance level of $p < 0.05$.

Model building

We utilized a maximum likelihood-fitted logistic regression model on complete observations only. Non-linear main-effect terms were fitted using fractional polynomials. Goodness of fit was tested using the Hosmer and Lemeshow test on a random sample, due to the tests excess sensitivity to large datasets [11, 12]. Four regression models were assembled. The first was built on all non-missing observations of TBI and strokes to test interactions. Three additional models were constructed to calculate the effect of RSI for TBI, ischemic and haemorrhagic stroke separately. Previous work using this same dataset showed that missingness were clinically insignificant and did not meaningfully impact estimates [4]. As such, no sensitivity analyses for the impact of missing data were conducted.

Interaction

This analysis tested how the components of RSI interact with stokes and TBI for survival in the RSI-only group. Any such interactions in the RSI-only group might indicate that RSI influences survival differently for strokes compared to TBI, suggesting that the brain trauma RSI evidence cannot be applied to strokes. Rapid sequence intubation consists of many elements including medications, intubation success proportions and number of attempts, scene time and time to intubation. All these factors were tested for interaction and all interactions are presented graphically in this text.

Medications assessed for interaction with TBI and strokes include atropine, midazolam, midazolam/morphine infusions and fentanyl, as only these medications had sufficient data permitted an interaction test. Furthermore, RSI is likely to directly impact blood pressure, pulse rate, oxygen saturation, Glasgow Coma Scale, respiratory rate, end-tidal carbon dioxide [4]. Therefore,

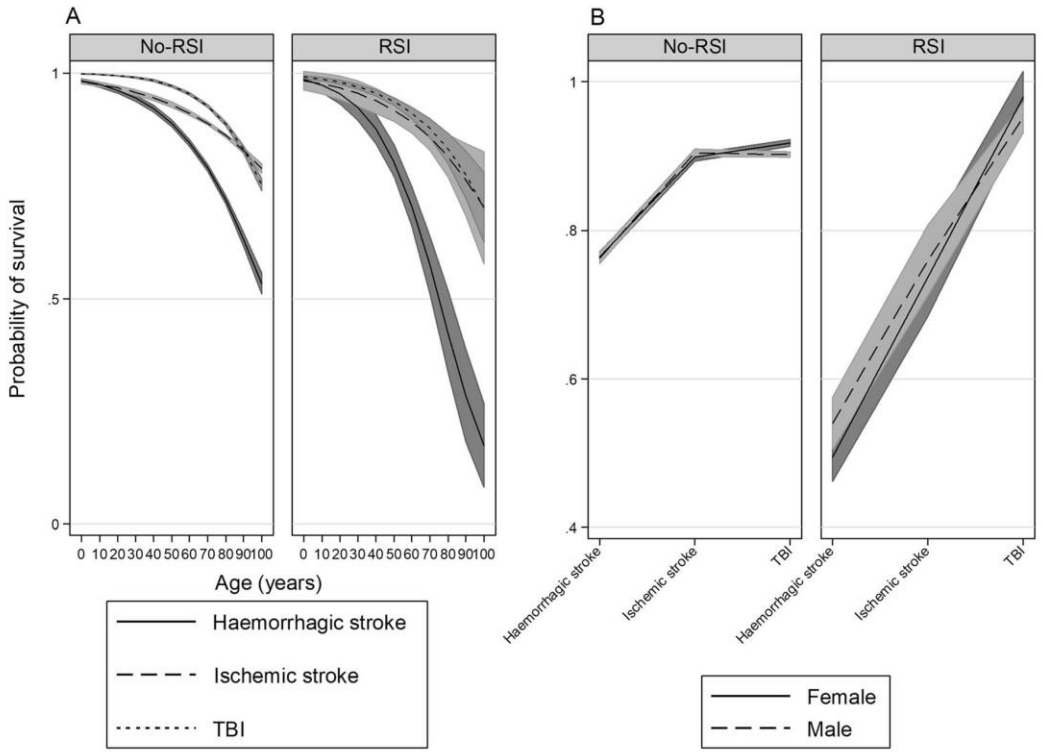

Fig. 2 Interactions of demographic factors in a cohort of strokes and TBI, RSI compared to no-RSI. a interaction of age and pathology. b interaction of sex and pathology

we also tested the interactions of vital signs. These vital sign changes were calculated by subtracting the final on-scene value from the first on-scene measurement [4]. All interaction terms that were statistically significant at a 5 % level were considered as evidence of interaction. Results of interactions are presented in the manner suggested by Knol and van Der Weele [13], and we present the relative excess risk due to interaction in supplementary tables [14].

Results

This cohort included 107,128 (Fig. 1) of which 1993 (1.9%) received RSI. A total of 80,324 (75%) had complete data of which 11,133 (13.9%) were diagnosed with haemorrhagic stroke and 26,754 (33.3%) with ischemic stroke and 42,437 (52.8%) with TBI. Baseline characteristics of the full-data cohort are compared in Table 1. The overall intubation success was 97.8% and first pass success was 89.6%, with no significant change in success over time for overall ($p = 0.40$) or first-pass ($p = 0.12$).

Overall outcomes

After removing missing data, 80,324 strokes and TBI were transported by ambulance of which 71,008 (88.4%) survived to hospital discharge. In an unadjusted regression those that had received RSI had 88% lesser odds of survival; OR 0.09 (95% CI 0.08 to 0.10; $p < 0.001$) compared to those patients that did not receive RSI. An adjusted regression analysis found no significant difference in survival for TBI, with − 0.7% lesser survival for RSI compared to no-RSI; OR 0.86 (95% CI 0.67 to 1.11; $p = 0.25$) (Additional file 1: Table S1A). Survival for haemorrhagic stroke was − 14.1% less for RSI; OR 0.44 (95% CI 0.33 to 0.58; $p = 0.01$) and was − 4.3%; OR 0.67 (95% CI 0.49 to 0.91; $p = 0.01$) lesser for ischemic strokes (Additional file 1: Table S1B and C). Model fit and performance statistics indicate good fit (Additional file 1: Table S3).

Table 2 shows that the decline in systolic blood pressure is tenfold larger for haemorrhagic strokes compared to TBI. Oxygen saturation increases more when RSI is utilized, and the largest rise is for ischemic strokes. Respiratory rate does not change meaningfully in the

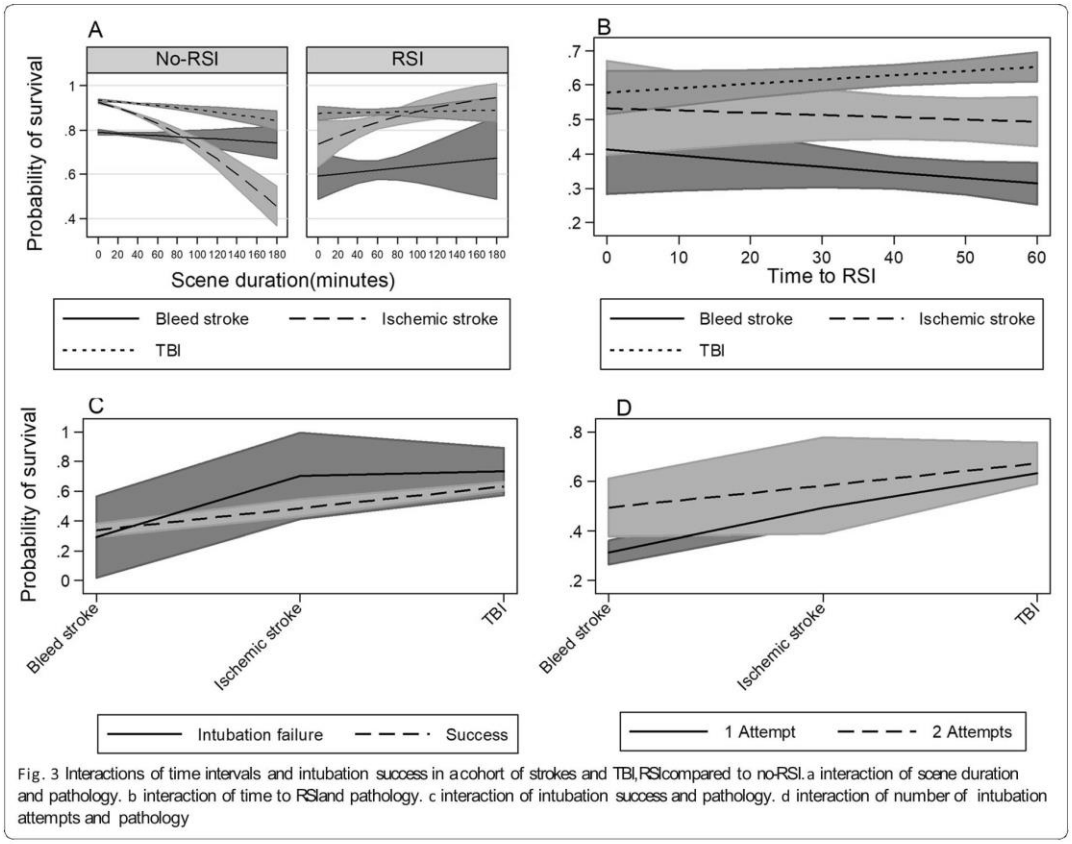

Fig. 3 Interactions of time intervals and intubation success in a cohort of strokes and TBI, RSI compared to no-RSI. a interaction of scene duration and pathology. b interaction of time to RSI and pathology. c interaction of intubation success and pathology. d interaction of number of intubation attempts and pathology

absence of RSI use, but there are six breaths per minute drop with RSI. Predictably, Glasgow Coma Scale decreases with RSI usage. For non-RSI patients pulse rate tends to decrease slightly on scene, but when RSI is utilized pulse rate increases, with haemorrhagic stroke double that of TBI and ischemic strokes.

Interactions

Here we report interactions that are statistically significant or borderline significant. All interactions are presented graphically in Figs. 2, 3, 4 and 5. For a complete report on all interactions, see Additional file 1: Table S2A to O.

Demographic factors

Age strongly predicted survival (Additional file 1: Table S1A to C). Age interacted with TBI and stroke in the RSI-only group (p = 0.02) (Additional file 1: Table S2A; Fig. 2a). A borderline insignificant interaction within the RSI group exist when comparing sex (p =0.06) (Additional file 1: Table S2B; Fig. 2b).

Prehospital time intervals and intubation success

No significant interaction for scene-time was found in the RSI-only setting (p = 0.18) (Additional file 1: Table S2C; Fig. 3a). Even so, there was a borderline significant difference in the slopes for ischemic stroke vs TBI (p = 0.06). The mean time-to-RSI was 39.4 min (SD = 24.8), but there was no significant interaction for time-to-RSI (p = 0.10) (Additional file 1: Table S2D; Fig. 3b). However, a borderline significant difference between the survival slopes of TBI versus haemorrhagic strokes was noted (p = 0.05). We found no evidence of interaction of intubation success (p = 0.49) (Additional file 1: Table S2E; Fig. 3c). Two or more attempts at intubation success was associated with increased survival for haemorrhagic strokes (p = 0.004), but not for ischemic strokes or TBI (Additional file 1: Table S2F; Fig. 3d). Nonetheless, both the number of

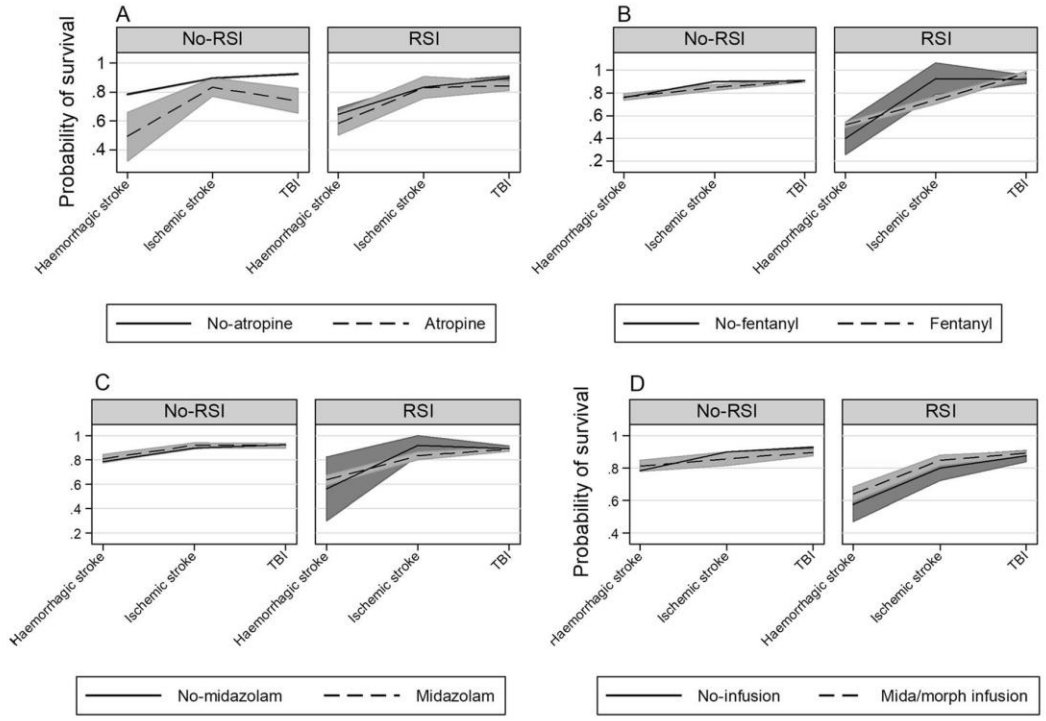

Fig. 4 Interactions of medications used with RSI in a cohort of strokes and TBI, RSI compared to no-RS. a interaction of atropine and pathology. b interaction of fentanyl and pathology. c interaction of midazolam and pathology. d interaction of midazolam/morphine infusion and pathology

intubation attempts and intubation success had low cell counts, limiting inferences from these two analyses.

Rapid sequence intubation medications

The interaction of atropine showed that survival was lower for TBI when atropine was used with RSI ($p = 0.001$) (Additional file 1: Table S2G; Fig. 4a). The interaction of fentanyl indicated that when fentanyl was used with RSI, survival is better for TBI ($p = 0.01$) (Additional file 1: Table S2H; Fig. 4b). No significant interactions for midazolam was apparent ($p = 0.34$) (Additional file 1: Table S2I; Fig. 4c), nor for midazolam/morphine infusions ($p = 0.31$) and ($p = 0.84$) (Additional file 1: Table S2J; Fig. 4d).

Changes in vital signs after RSI use

Survival decreased for haemorrhagic strokes and TBI as systolic blood pressure increased (Additional file 1: Table S1A to C). No interaction of systolic blood pressure for the RSI-only group is apparent ($p = 0.61$) (Additional file 1: Table S2K; Fig. 5a). No interaction was found for changes in respiratory rate ($p = 0.52$) (Additional file 1: Table S2L; Fig. 5b). For changes in $ETCO_2$ with RSI use, no interaction is obvious ($p = 0.91$) (Additional file 1: Table S2M; Fig. 5c). No interaction for changes in SPO_2 and TBI and stroke was found in the RSI-only setting ($p = 0.91$) (Additional file 1: Table S2N; Fig. 5d). For those that receive RSI significant differences exist between the stroke and TBI slopes of pulse rate change ($p = 0.03$) (Additional file 1: Table S2O); Fig. 5e).

Discussion

This analysis shows that RSI interact with strokes and traumatic brain injuries in terms of survival, indicating that the TBI evidence might not be useful to guide stroke RSI. As anticipated, this implies that the stroke patient differs from the TBI patient enough that RSI components impacts survival differently for these two pathologies. Significant interactions in the RSI-only group included number of intubation attempts, atropine, fentanyl, pulse rate and perhaps scene time, time to RSI as well as the age of the patient. Another suggestion that TBI evidence might not transferable is the difference in survival between the strokes and TBI for RSI. Haemorrhagic strokes have 14% lesser RSI survival, compared to

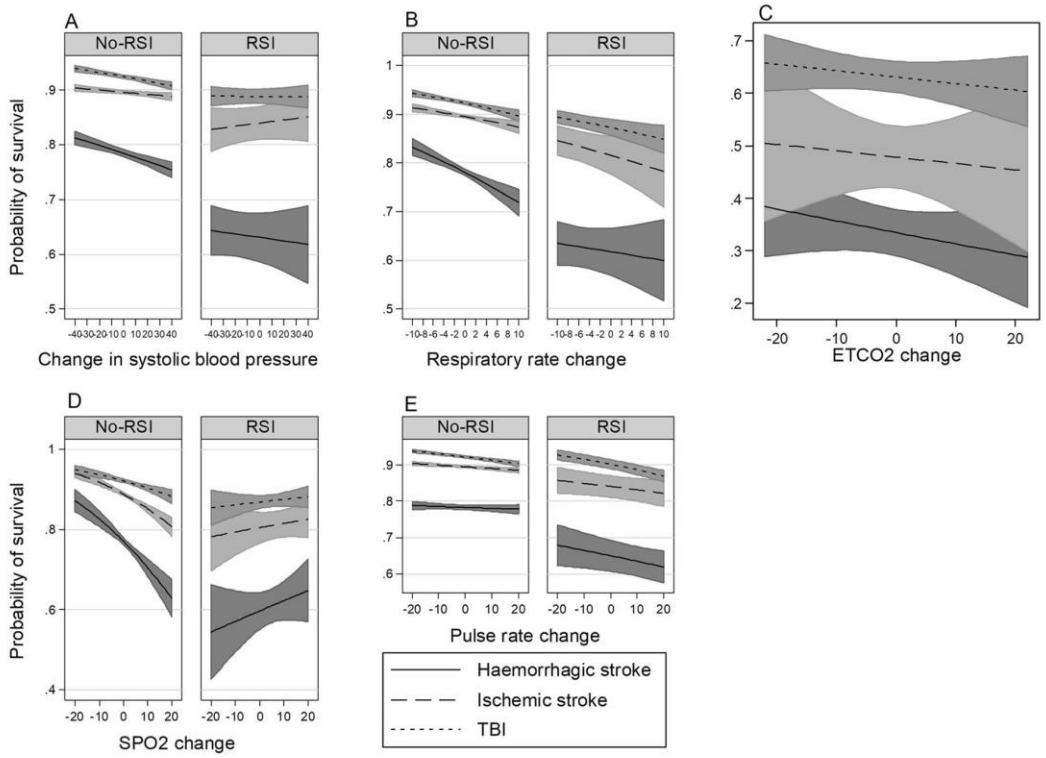

Fig. 5 Interactions of changes in vital signs in a cohort of strokes and TBI, RSI compared to no-RSI. a change in systolic blood pressure and pathology. b interaction of respiratory rate change and pathology. c interaction of ETCO2 change and pathology. d interaction of SPO2 change and pathology. e interaction pulse rate change and pathology

ischemic stroke of 4% and TBI a lesser than 1% survival difference between RSI and no-RSI.

Large differences in the changes in systolic blood pressure with RSI use are evident when comparing strokes and TBI. The largest decreases in RSI-related blood pressure were found in haemorrhagic strokes, and the least in TBI. Survival follows this pattern too, with haemorrhagic stroke the poorest survival compared to TBI the best. However, it is not clear that these decreases in blood pressure are the causes of poorer survival. Our analysis show that decreases in blood pressure with RSI was not associated with a significant decrease in survival. This finding of no decrease in survival after a decrease in blood pressure with RSI is mirrored in the results of the GOLIATH trial, which compared conscious sedation to general anaesthesia in ischemic stroke [15]. In the GOLIATH trial general anaesthesia caused a greater mean blood pressure drop compared to the conscious sedation group, similar to the drop in systolic blood pressure found with RSI in our analysis. Despite the decreased blood pressure caused by general anaesthesia in the GOLIATH trial, no decreased survival with such a blood pressure drop was found. Interestingly, survival seems to *increase* for haemorrhagic stroke after decreased blood pressure, but this effect was not statistically significant. This suggestion of increased survival with decreasing blood pressure after clinical interventions in haemorrhagic strokes have been found in other studies [16].

Age could be the most important driver of the differences in RSI survival between strokes and TBI, not blood pressure. Age decreases survival for both strokes and TBI, but the survival decrease is much more rapid for haemorrhagic strokes. These differences in the steepness of decline of the age slopes are important when one considers that almost three quarters of all stroke RSI in our analysis were haemorrhagic strokes, and the average age of these haemorrhagic stokes were 65 years, compared to TBI of 43 years. Given this large difference in age between TBI and haemorrhagic stroke for those that received RSI, and keeping in mind the much steeper decline with age in survival when comparing haemorrhagic stokes to TBI, the large difference between the survival for haemorrhagic stroke compared to TBI is unsurprising. Large decreases

in survival with advanced age for patients with haemorrhagic strokes are consistent with another Australian study [17].

Other important interactions in the RSI-only group were evident. An increased number of intubation attempts were associated with increased survival for haemorrhagic strokes. This surprising and possibly confounded effect could result from less obtunded patients needing more intubation attempts. Another significant interaction was atropine, with lower survival for TBI when atropine was used. The mechanisms of this finding are unexplained. Furthermore, the interaction of fentanyl on the pathologies showed TBI have better survival when fentanyl is used and ischemic strokes worse survival with fentanyl use. Fentanyl is used to blunt the hemodynamic effects of intubation [18], but causes a decrease in mean arterial pressure [19]. it is possible that the blood pressure effects of fentanyl could be the cause of this medications impact on survival in this analysis. Furthermore, our analysis also found an interaction between pulse rate and pathology, with both strokes and TBI associated with decreased survival with increased pulse rate. We believe that the effect of pulse rate is mainly through the impact of blood pressure changes, and not pulse rate itself. Also, RSI use is associated with an apparent reversal of the deleterious effect of staying on scene longer. This could be due to potential benefits of RSI or perhaps a selection effect: patient that lived long enough to receive RSI at later scene times would cause an association of better survival with longer times on scene.

It is a strength of our study that our measures of prognostic risk due to illness severity and comorbidities together predicted survival well with an area under curve of 0.83, which is higher than the 0.75 that would provide evidence of adequate risk adjustment [20]. Even so, it is possible that these results are still somewhat biased due to unmeasured confounding. Another strong point of our study is that it had a very large sample size, and consequently good statistical precision. This study has limitations. Firstly, the utility of observational methods to reveal treatment effects are limited, especially if the anticipated effect is small [21]. Secondly, we could not compare good neurological survival, which would have been a more suitable. Thirdly, we calculated the change in vital signs by subtracting the first values upon scene arrival from the last values before handover at the emergency department. Additionally, we believe that comparing the first vital signs measured upon arrival at the patient's side to the last vital signs (measured after all prehospital treatments were given) would show the impact of the effects of RSI on these vital signs after adjustment for confounders. Our data did not allow for a comparison of vial sign changes *during* RSI. We did not consider non-linear interaction terms due to restrictions in the sample sizes of the RSI group, although we anticipated non-linear effects for many variables.

Conclusions

Rapid sequence intubation and related factors interact with stroke and TBI, which implies that RSI effects stroke survival differently from TBI. If RSI impact survival differently for strokes compared to TBI, then perhaps the TBI evidence cannot be used for stroke RSI. A trial comparing RSI to no-RSI in the out-of-hospital setting is urgently needed.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12873-020-0303-9.

Additional file 1: Table S1. A. Estimates of a logistic regression model of RSI adjusted for covariates in 42,437 traumatic brain injuries. B. Estimates of a logistic regression model of RSI adjusted for covariates in 29,457 ischemic strokes. C. Estimates of a logistic regression model of RSI adjusted for covariates in 14,374 haemorrhagic strokes. Table S2. Rapid sequence intubation effect modification of factors. Table S3. Model Fit and performance statistics.

Abbreviations

GCS: Glasgow Coma Scale; RSI: Rapid Sequence intubation; TBI: Traumatic brain injury

Acknowledgements

We are grateful to the staff at the Centre for Victorian Data Linkage as well as Salman Sabir at Ambulance Victoria for their assistance in obtaining the data for this study.

Authors' contributions

PFF conceived of the study. PFF, PAJ, MB, SB and KS all contributed to the methodological design of this research. KS and PFF collected data and PFF analysed all data. PFF, PAJ, MB, SB and KS interpreted the data and also contributed to the manuscript. All authors have read and approved the manuscript. PFF takes responsibility for the paper as a whole.

Funding

No funding for this study.

Availability of data and materials

Data is not available due to privacy concerns of patients.

Ethics approval and consent to participate

Monash University Human Research Ethics Committee provided ethics approval (ref. no. 8618).

Consent for publication

Not Applicable.

Competing interests

Co-author Paul Andrew Jennings is a member of the editorial board (Associate Editor) of BMC Emergency Medicine.

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Received: 19 November 2019 Accepted: 13 January 2020
Published online: 28 January 2020

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Publisher's Note

6.4. Principle findings and conclusions

This analysis found no significant difference in RSI survival for TBI, noting a –0.7% comparatively lower survival compared to no-RSI. At the same time, haemorrhagic and ischaemic stroke experienced –14.1% and –4.3% lesser survival for RSI versus no-RSI, respectively. Significant interactions in the RSI-only group for age, number of intubation attempts, atropine, fentanyl, pulse rate and scene time, and time-to-RSI together suggest that intubation affects survival differently for TBI versus stroke. As RSI interacts with both pathologies, this indicates that RSI affects stroke survival differently from brain injury. If this is the case, then conceivably the TBI evidence cannot be utilised for stroke RSI. Nonetheless, a trial comparing RSI to no-RSI in out-of-hospital settings is immediately required.

Chapter 7: Key findings, implications and recommendations

7.1 Interpreting the findings and suggestions for further investigation

This thesis, which includes published work, investigated the causal link between RSI and NTBP survival using observational research methods. Now, Chapter 7 discusses the key findings and interprets the results, as they affect clinical practice. Detailed suggestions are also made for future research.

7.2 NTBPs are common in RSI, and vice versa

7.2.1 Key findings

Although RSI is an advanced airway technique with the potential to save lives, its complexity and use of medications, which paralyse patients and stop breathing, mean that many adverse events are possible. For example, failure to intubate the trachea and inadvertent oesophageal intubation can cause hypoxic brain damage and death.[66-68] Additionally, alterations in blood pressure after laryngoscopy and pre-medications, pneumonia, hypo/hyperoxia, hypo/hyperventilation, cardiac arrhythmias, adult respiratory distress syndrome and atelectasis, along with dysphagia associated with intubation, are all possible causes of decreased survival.[51,64,69-72] In light of so many potential risks that could increase mortality and morbidity, the need for high-quality evidence is necessary to support RSI.

Chapter 1 reported the results of a systematic review that clearly showed the lack of research supporting RSI in NTBP, both for emergency departments and out-of-hospital settings. This review did find some literature that reports survival for stroke and seizure patients receiving RSI, but none were methodologically rigorous enough to show a causal link between procedure and survival. Quality assessments of these observational studies found that all had failed to adequately account for the acute sickness of RSI versus no-RSI groups. Following the systematic review and meta-analysis, it is evident that no high-quality evidence exist to supports intubation in

non-traumatic pathologies.[2] That said, the RSI groups across the literature were typically *sicker*. When acutely ill patients receive a treatment because they are sicker, a type of confounding result, called 'confounding by indication',[73-76] thus, introducing bias. This is particularly prevalent in observational studies in emergency medicine, especially advanced airway research.[62,63,77]

This prompts several questions. First, is high-quality evidence needed if RSI were rarely used in NTBPs? Would it matter if RSI evidence were lacking if paramedics utilise RSI only infrequently? Evidently, if the disease burden of non-traumatic cases were large and if RSI were frequently used in these pathologies, then the urgency of quality evidence becomes very important. Chapter 1 discussed the findings of a systematic review that showed how endotracheal intubation is commonly used in emergency departments and out-of-hospital settings to secure the airways of NTBP patients.[2] It made a case that most of these endotracheal intubations are likely RSI, and showed that RSI proportions by paramedics range from 48% to 55% for NTBP, such as strokes and seizures.[78-80] When comparing the out-of-hospital RSI to emergency-department based intubations, the intubation proportions proved similar. However, comparisons with emergency departments must proceed cautiously, given the small number of studies that report RSI in out-of hospital settings. Even so, it is clear that a sizable proportion of NTBPs receive RSI.

While Chapter 1 shows that RSI is prevalent in the emergency NTBP population, it does not follow that NTBP would necessarily be common in RSI recipients. To demonstrate this apparent paradox, consider a scenario in which the incidence of NTBP in a population is very low. Even if RSI were commonly used in a low-incidence NTBP, the annual RSI prevalence in NTBP itself would also be low. Therefore, to obtain a complete picture of the disease burden and utilisation of RSI, it is important to invert the numerator and denominator, and ask how common NTBPs are in those that receive intubation. As such, Chapter 2 enumerates the prevalence of NTBPs in RSI recipients over an eight-year period.[3] Seven Melbourne hospitals contributed data, from which it clarified that 58% of all paramedic RSI were performed on NTBP patients—69% of whom survived to hospital discharge. The survival and prevalence in the RSI group varied greatly depending on the pathology. Strokes were the most common and had the poorest survival to discharge (37%)

compared to the second most common NTBP (toxicity/toxic encephalopathy), which had very high survival (98%).[3] Additionally, the statistical model found that no out-of-hospital clinical intervention or prehospital time interval predicted survival significantly, but that GCS, duration of mechanical ventilation, age, ICU length of stay and comorbidities did predict mortality. Thus, the systematic review in Chapter 1 shows that RSI is common in NTBP, while the Melbourne-based cohort study in Chapter 2 demonstrates that NTBP is common in RSI. The NTBP disease burden is substantial, especially for strokes, and RSI is often used. Good evidence that supports RSI use remains critical.

7.2.2 Implications

The findings from Chapters 1 and 2 indicate that RSI use is common in NTBP (especially for stroke), and that strokes have typically poor survival, particularly if haemorrhagic in nature. Figure 7.1 graphs the survival of NTBP following RSI treatment across Melbourne, Australia.

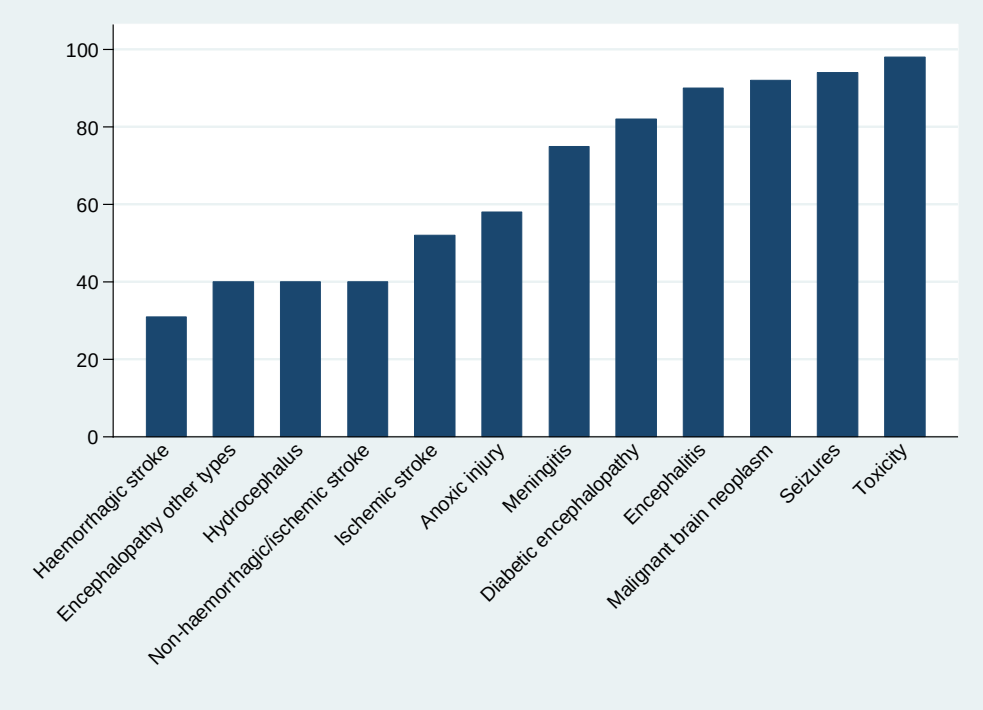

Figure 7.1. Survival of NTBP that received paramedic RSI in Melbourne, Australia.

Figure derived from the cohort in Chapter 3.

Stroke accounts for 10% of global deaths[81] and almost 5% of all disability-adjusted life years.[2,3] Not only is stroke a large cause of death and disability worldwide, the first two chapters show that stroke RSI is the most important NTBP that receive paramedic RSI in terms of its prevalence and mortality, and the implications of the high prevalence and frequent use of RSI in stroke is that creating an evidence base for stroke RSI is a high priority. Such high incidence and frequent clinical use exemplify just how crucial building a solid evidence base is for stroke intubation.[1] Indeed, data from the Bernard et al. paramedic brain trauma trial might not be applicable to stroke or any other NTBP RSI.[1-3] The chief implication following systematic review and the cohort study in Chapter 2 is that the disease burden remains high and that RSI is commonly used, but that paramedic RSI for NTBP is without support. This is especially true for stroke RSI, which is the most immediate and pressing problem, and for which the need for strong evidence is most necessary.

7.2.3 Recommendations

First, since no high-quality data readily support NTBP RSI—and given that NTBP is so common in paramedic intubation (and vice versa)—the need for evidence is increasingly critical. This is especially true, as the brain trauma literature cannot be applied to the non-trauma clinical domain. Future research should focus on strokes, as they are the most common pathology that receives RSI, especially if haemorrhagic.

Both observational trials and RCTs would be suitable to study RSI in NTBP. The latter would provide the most robust evidence, but observational research is certainly complementary, as it offers 'real-world' evidence without the restrictions and lack of external validity that typically burden trials.[56,57]

A randomised trial *is* feasible, as the successful completion of Bernard's brain trauma RCT suggests.[39] However, their efforts were possibly undermined due to a reliance on secondary outcomes,[47] and possibly also lack of power. A much larger trial for NTBP would prove effective but more difficult to undertake. Thus, it is recommended that a qualitative study precedes the trial to test feasibility in out-of-hospital settings. Problems with one Western Australian paramedic adrenaline trial

suggest that enrolment problems in domestic contexts could be potentially problematic and scupper such an attempt.[82] To test feasibility of a large RCT, a pilot trial should precede the pivotal RCT,[83] as was done in the Benger et al intubation in cardiac arrest experiment.[84]

Concomitant and perhaps preceding such an NTBP trial, observational methods to study the treatment effect of RSI can be used. However, given the potential for confounding by indication in RSI (wherein only sicker patients receive treatment), bias may become a key limitation.[74-76] An effective way to account for such data distortion in advanced airway research is to adjust for illness severity and comorbidity scores.[63,85] For strokes, the National Institutes of Health Stroke Scale (NIHSS) or similar would suffice,[86] and commonly used comorbidity scores such as the Charlson comorbidity index or Elixhauser score can work.[87-89] If the combined illness severity and comorbidity score is adjusted for, and the area under curve exceeds 0.75, then such a study is well protected against the confounding effect by indication.[76] Illness severity scores for seizures and other NTBP are *not* routinely available in Australian datasets, further limiting adjustment by these factors in future RSI studies. Such illness severity data would have to be prospectively collected.

7.3 RSI in strokes is associated with decreased survival

7.3.1 Key findings

Chapters 2 and 3 showed that strokes are the most common NTBPs with the highest mortality of all neurological pathologies receiving RSI. As such, strokes are arguably the most important NTBP for which paramedic intubation is used. These two chapters argued that future research should begin with testing the efficacy of RSI in strokes, and that TBI RSI evidence might not apply to strokes. Consequently, Chapter 4 presented the results of a large data-linkage cohort study of strokes over a 10-year period covering Victoria, Australia. Since the feasibility of a trial was not yet clear, this study utilised observational methods that mimic aspects of an RCT to avoid the bias that results from confounding by indication. Specifically, this large stroke linked-dataset was used to create a propensity score-matched cohort, which is

an efficient observational method to sidestep potential bias due to measured confounding.[90]

Results from this propensity-matched cohort indicate that paramedic RSI might cause decreased survival for intubation in stroke. The direction of effect (of decreased survival) is believable, as indicated by robust testing for the potential effect of unmeasured confounding. However, the exact magnitude of this RSI treatment effect in stroke remains uncertain due to possible residual confounding. This study also shows a substantially larger decrease in systolic blood pressure for RSI recipients compared with no-RSI. Additional derangements in CO_2, oxygen, pulse rate and respiratory rate found here could explain this decreased rate of survival.[1]

7.3.2 Implications

Increased mortality in out-of-hospital stroke RSI is a cause for concern, as it disagrees with the apparent benefit that intubation confers in TBIs. The Bernard trial found a 3% increase in survival-to-hospital discharge in favour of RSI,[39] but this apparent benefit of paramedic intubation in brain injury does not seem to be conferred to stroke. Given that the stroke estimate from the propensity-matched cohort is lower for RSI (OR 0.61), the implication following analysis in Chapter 4 is that intubation does not benefit strokes and TBI equally, and RSI does not seem to affect ischaemic stroke as it does haemorrhagic stroke. The RSI survival for ischaemic stroke was superior to its haemorrhagic counterpart, with an OR 0.66 (95% CI 0.40 to 1.07; $p = 0.09$). If the results of the propensity-matched stroke RSI study were unbiased, then this suggests that the TBI evidence cannot be applied to stroke RSI. However, what are the mechanisms that underpin the difference in RSI survival between strokes and TBI? Determining the exact causes that drive survival disparities when comparing the two would provide informed reasons through which to reject RSI in TBI evidence and apply it to incidence of stroke. Indeed, the propensity-matched cohort study suggested that blood pressure changes might drive such differences, in that the RSI cohort experienced a significantly larger drop of 10 mmHg in on-scene blood pressure compared to no-RSI.

7.3.3 Recommendations

Results of the propensity-matched cohort study in Chapter 4 cannot be used to guide clinical practice, but do serve to show that paramedic RSI can cause decreased survival in stroke. The need for an RCT is even clearer following this matched study.

If RSI affects survival differently when comparing NTBP and TBI, then the mechanisms that underlie these differential effects need clarification. Changes in blood pressure are one such potential mechanism outlined in Chapter 4. Essentially a collection of treatments, RSI consists of many factors such as the number and success of intubation attempts, paralytic and sedative/hypnotics drugs, opiates and numerous other medications. The RSI procedure also involves ventilator parameters such as oxygen fraction, and the oxygen saturation that results from these fractions, tidal volume and rate, and $ETCO_2$. All these composite factors should be tested when used within RSI to gauge their direct effect on survival or through such mediating factors as blood pressure, level of consciousness, respiration and oxygenations. If any prove influential, then it would clarify why (and if) the TBI evidence can be applied to NTBP RSI.

7.4 Can the TBI evidence for paramedic RSI be applied to NTBPs such as stroke?

7.4.1 Key findings

Chapter 5 presented the results of a large cohort of strokes and chapter 6 also included TBI, derived from data linkage of in-hospital and out-of-hospital records. Chapter 5 showed that decreases in systolic blood pressure in a RSI cohort does not seem to cause poorer survival, and the results of this cohort study agrees with in-hospital anaesthesia RCTs. In chapter 6 significant differences in survival-to-hospital discharge were found when comparing strokes to TBI. Specifically, haemorrhagic stroke has an almost 13% lower chance of survival following RSI compared to brain injury. Brain trauma RSI by paramedics showed no significant difference in survival when compared to no-RSI, neither from a statistical nor clinical perspective. Overall, this observational study demonstrated that strokes—especially if haemorrhagic in nature—have poorer survival rates when receiving RSI compared to TBI. Further,

some mechanisms related to intubation could cause marked survival differences between stroke and TBI, thus, implying the unreliability of TBI evidence for stroke RSI.

To highlight the intubation-related mechanisms that could cause such discrepancies, Chapter 6 reported the results of a study on interactions in an RSI-only group of RSI components. Significant interactions in this sample for age, number of intubation attempts, atropine, fentanyl, pulse rate and scene time, and time-to-RSI imply that RSI affects survival differently for TBI versus stroke. Stated differently, these interactions of the components of RSI demonstrated that RSI itself may well impact survival differently for TBI compared to strokes. Notably, this study made a strong case that the biggest cause in survival difference is not due to medications or derangements in blood pressure, pulse, oxygen or CO_2 levels, but mostly due to the effects of age. Indeed, age decreases survival for both pathologies, but the rate of reduction is much more rapid for haemorrhagic strokes when RSI is used. Differences in the steepness of decline against age slopes are important given that the average age of haemorrhagic stroke is 65 compared to TBI at 43 years. Such a large difference in age for those that received RSI, and the greatly sharper decline in survival when comparing haemorrhagic stokes to TBI could be the cause of the large survival differences for haemorrhagic strokes compared to TBI.

7.4.2 Implications

Interactions in the RSI group between stroke and TBI for age, number of intubation attempts, atropine, fentanyl, pulse rate, scene time and time-to-RSI show RSI potentially causes distinct rates of survival for stroke compared to brain injury. Furthermore, decreases in systolic blood pressure with RSI might not be implicated as a cause of poorer survival, contrary to preconceptions. These two studies strongly suggest that researchers cannot use the evidence from TBI RSI and apply it to stroke, and that blood pressure changes might not be the cause of poorer survival in stroke RSI. Consequently, the two most rigorous RSI studies to date—the historically controlled trial by Davis et al. and the Bernard et al. RCT—are not transferable to stroke RSI.[39,45,91] This lack of transferability means that more rigorous research is

needed, ideally in the form of an RCT comparing paramedic RSI to no-RSI—not only for strokes, but also for all NTBP.

7.4.3 Recommendations

Both an RCT and observational methods can be used to generate evidence to support NTBP RSI.[92] Classical observational analytic techniques such as regression adjustments have limited application for neurological pathologies, as made-for-purpose illness severity scores are poorly collected in Australian prehospital datasets. The supplementary material in Chapter 4 (see Appendix C.3.1) shows a causal graph for stroke RSI that demonstrates the importance of adjusting for illness severity. Stroke severity scales such as the NIHSS,[86] seizure scales such as Chalfont Seizure Severity Scale[93,94] and other NTBP are not routinely collected prehospitally. Since the anticipated benefit of RSI is small, any residual illness severity will cause confounding by indication and, thus, bias results to the extent that such studies become inadequate.[56,57] Therefore, inability to adjust for illness severity in NTBP airways research severely limits research using traditional means. For observational research to show true causal effects of RSI, use of natural experimental methods is recommended. For an RCT, a pragmatic trial is likely optimal, as described in Section 7.4.5.

7.4.4 Natural experimental methods

Natural experiments can produce results that are as true as an RCT.[95] The effect of RSI in NTBP such as stroke can be estimated in an unbiased way using natural experimental methods such as regression discontinuity and instrumental variables.[96,97] To demonstrate how regression discontinuity might be used, consider that Ambulance Victoria clinical practice guidelines recommend paramedics withhold RSI if a patient has less than an estimated 10-minute transport time to hospital.[36] This cut-off is expected to increase the probability of RSI for those at greater distance and likewise decrease the likelihood at closer proximity. Patients close to and on either side of the 10-minute mark are expected to be similar in all confounding factors that could affect their survival, similar to a randomised experiment.[98] Therefore, one can compare all the patients on one side of the 10-minute mark (who are very close to this cut-off) against those on the other side. For

example, a study could examine patients with a nine-minute transport time against those with 11 minutes. Both samples should be very similar in all important confounding factors, but the latter (more distant) group is more likely to receive RSI. Therefore, transport times around the 10-minute cut-off would serve well as a pseudo-randomisation device. Further, it is recommended that researchers limit analysis to transport within either side of the 10-minute mark or select these bin widths using data-driven methods. Two-stage least-squares regression could be used to predict a local average treatment effect as risk differences.[99]

An alternative to regression discontinuity is to use instrumental variables. This natural experimental technique employs variables much like a coin flip does in an RCT,[99] as it only predicts the treatment of interest (such as RSI) but is neither associated with any other variable, nor the outcome.[98] An example of an instrumental variable that predicts RSI in strokes is calling for MICA paramedic backup and subsequent availability. When a paramedic crew attends to a stroke or other NTBP and notices that the severity of sickness might require RSI, it typically calls upon MICA assistance. However, potential unavailability at the time means that paramedics have no choice but to transport (likely unconscious) patients to hospital without RSI, despite being suitable for intubation. Hence, the variable 'MICA availability' would be a true instrumental variable (Figure 7.2), particularly as it is not associated with any other variable or the outcome, and adjusting for it using two-stage least-squares regression will produce unbiased RSI estimates—assuming that the conditions for analysis are met.[99,100]

Natural experimental methods were not employed in this thesis, as the RSI sample size was too small and, thus, prone to produce biased and unstable estimates.[101] As time progresses, the RSI numbers for AV will increase, making instrumental variable methods more suitable for use, and offering a viable alternative to RCTs.

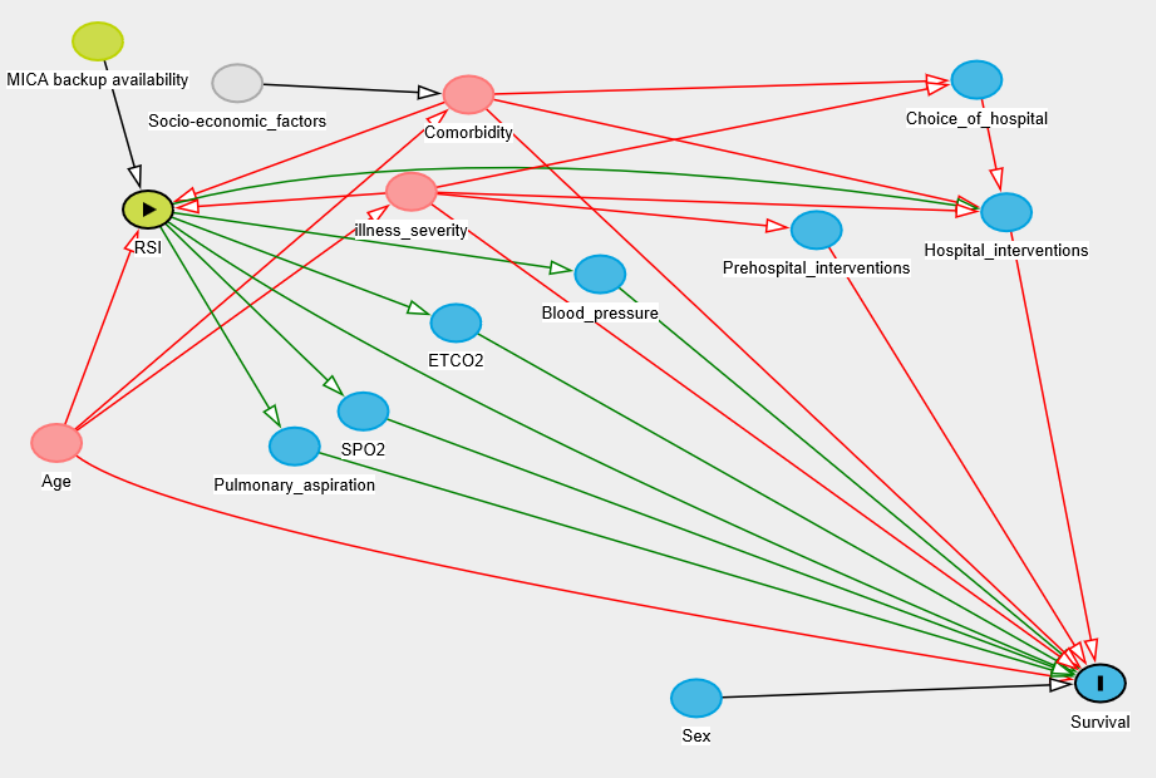

Figure 7.2. Directed acyclic causal graph showing MICA backup availability is a true instrumental variable.

7.4.5 RCT

Chapter 6 presented the results of a cohort study that revealed evidence from RSI in TBI cannot be extrapolated to NTBP. For this reason, it is essential to conduct a randomised trial that provides evidence for RSI in strokes and other neurological pathologies. There are other reasons why the TBI evidence is not suitable to inform RSI in NTBP. Firstly, the Bernard RSI trial might not be adequate to inform RSI in brain trauma (for which it was designed). Although a landmark trial,[47] its limitations are such that it might not guide TBI RSI and neither guide NTBP airway management. It was Fitzgerald et al. who recently argued against the Bernard trial, claiming it suffers from selecting secondary end points as important results and fails to account for multiple comparisons.[47] Furthermore, the researcher argue that the Bernard trial was underpowered to show a statistically significant difference survival to hospital discharge. To show this, the researcher calculated a confidence interval for the survival to discharge for the Bernard trial, which was not reported in their publication. Bernard reported a three percent benefit in terms of survival to hospital

discharge in favour of RSI, and the 95% confidence interval calculated ranges from -7% to 13%. This very wide confidence interval implies lack of power due to a small sample size, and shows that RSI can harmful or beneficial for traumatic brain injuries in terms of survival.

It is apparent that the TBI evidence for RSI might not support the use of RSI in the brain trauma, much less as an advanced airway method for NTBP, as chapter 6 indicates. Indeed, natural experimental methods were proposed, but these depend on collecting data for the instrumental variables or having a suitable number of RSI for regression discontinuity. Since the current evidence for RSI is unreliable and cannot be applied to NTBP—even if the evidence were reliable—it is clear that an RCT garners increasing priority.[1-3] Hence, the methodological elements of such a trial are as follows.

Foremost, a pragmatic RCT is recommended.[102] Typically, trials are selective and suffer from problems with external validity,[103,104] but a pragmatic trial is designed to show the real-world effectiveness of intervention in wider patient groups.[102] Typically completed without strict inclusion criteria, such a trial has been the design of choice for recent paramedic intubation work in cardiac arrest.[105] Chapter 3 showed that strokes and seizures are by far the most frequent NTBPs that receive paramedic RSI. Given that no reliable evidence supports RSI in brain trauma or NTBP, a pragmatic trial should ideally include *all* RSI for any pathology, including TBI.[106,107] A trial for paramedic RSI for NTBP-only would be practically difficult, as paramedics cannot randomize strokes in a trial, since they cannot reliable diagnose strokes prehospitally.[108] A trial that enrols all RSI, regardless of underlying pathology, can then analyse these subgroups separately.

Third, some of the pathology subgroups, such as for meningitis or brain neoplasms, will be unavoidably small, given that they receive few RSIs in Victoria.[3] An RSI trial will be underpowered for these samples, but could be powered for the most important pathologies, such as ischemic stroke, haemorrhagic stroke and TBI. Table 7.1 present various sample sizes for a pragmatic trial with a survival-to-discharge, calculated for stroke and TBI and a variety of survival differences

between the groups compared. Consideration should be given to survival with good neurological function as alternative primary or as a secondary outcome.

Table 7.1: Sample Sizes (per Arm) for a Pragmatic RSI Trial at 5% Significance and 80% Power for Survival to Discharge

Difference in survival between RSI and no-RSI groups	Sample size for ischaemic stroke◊	Sample size for haemorrhagic stroke©	Sample size for TBI*
3%	4,359	4,262	3,941
5%	1,569	1,543	1,398
7%	800	791	702
9%	483	480	417
11%	322	322	274

* Baseline survival of TBI at 64%; © Baseline survival of haemorrhagic stroke at 41%; ◊ Baseline survival of haemorrhagic stroke at 48%

Fourth, out-of-hospital trials of intubation in cardiac arrest show that intubation benefits are likely minor.[84,105,109,110] The Bernard trial suggests that the survival to discharge is also likely small, with a 3% benefit noted for intubation in TBI.[39] Although the cohort study in this chapter suggests that survival for ischaemic stroke might be 4% lower for RSI and 14% less for haemorrhagic cases, these observational estimates cannot be used to calculate a sample-size calculation, as they are likely confounded by residual illness severity or other factors. Thus, a pilot trial would best inform a sample-size calculation for a later pivotal trial.[111] In the literature, Benger et al. used such a study to guide sample size for subsequent RCT in intubation of cardiac arrest, which proved the value of piloting within the context of advanced airway research.[84,109]

If the survival benefit of RSI proves to be small (as suggested in the Bernard trial), then an intubation study will be unavoidably long in duration, as the sample size will be large (Table 7.1). As such, a 3–5% survival benefit (or harm) is the most likely survival difference, meaning that a pragmatic RSI trial would be ≈ 1,569 to 4,359 patients per arm or a total of 3,138 to 8,718. Alternatively, if an outcome such as good neurological survival is used, the sample size might be as low 269 per arm or 538 in total, assuming that the likelihood of a positive outcome is the same in stroke

as it is in TBI. If enrolments are at 300 to 500 RSI annually, a trial might take between two and 10 (or more) years, depending on the chosen outcome. For these reasons a trial should use good neurologacl survival as the main outcome, and power the trial according to this outcome.

Finally, small pathology subgroups and equally small numbers of annual RSI make for small sample sizes in trials. However, lack of adequate power does not preclude a conducting trial.[112,113] An RSI study with survival-to-discharge as the main outcome and a sample of a 1,000 might not be large enough if statistical significance were essential, but it would still provide the best evidence on RSI-acquired brain injuries to date, given its comparatively (4–5 times) larger size to Bernard's trial. Likewise, it would take less than five years to conduct, considering that the number of RSIs in Victoria is ≈ 300–500 annually.

7.5 Conclusions and summary of findings

Non-traumatic brain pathologies are a common cause of morbidity and mortality, and are frequently treated by endotracheal intubation techniques such as RSI in the emergency milieu. This research demonstrates that RSI is commonly used for NTBP in the emergency department and out-of-hospital setting. It is also true that in Victoria, Australia, NTBP such as stroke comprise most of the RSI by paramedics. Despite RSI being commonplace, no high quality evidence such as a randomized controlled to support RSI for NTBP is available.

In this thesis, the researcher showed that stroke is the most common pathology that receives RSI in Victoria, Australia. Haemorrhagic strokes are the most common stroke type that receive paramedic RSI and has the highest mortality. It is evident from the cohort study in chapter four that observational research to estimate the treatment effects in stroke RSI would need to account for illness severity and comorbidity, and a matched cohort presented in chapter four showed that RSI in haemorrhagic strokes have poorer survival compared to ischemic strokes, but that RSI in both types of strokes fare worse than not receiving RSI at all. The propensity matched cohort study suggested that RSI might be a cause of decreased systolic

blood pressure on scene, and it is speculated that alterations in blood pressure are a cause of poorer survival in stroke.

Alterations in blood pressure as cause of decreased survival after RSI in stroke proved an unlikely causal factor, as the studies in chapter 5 shows. Additionally, chapter 6 made a case that RSI impact survival differently for strokes compared to TBI, and that the brain trauma evidence base cannot be used to inform the use of RSI in NTBP. It is evident that a randomized controlled or observational research utilizing rigorous methods be used to generate a new evidence base for NTBP. In this thesis I suggested that natural experimental methods such a regression discontinuity and instrumental variable analysis might provide "real world" evidence to support RSI, but ultimately a trial would be needed. A pragmatic randomized controlled trial is possible to do in Vitoria, Australia, but might take as long as a decade, depending on the sample size required which would make adequately powered trial prohibitively difficult. A trial that is unavoidably underpowered would not be without use to guide clinical practice, and would be worth conducting.

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Appendices

Appendix A: Monash University Human Research Ethics Committee registration for Chapter 3

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Confirmation of Registration

This is to certify that the project below is now registered with the Monash University Human Research Ethics Committee under the Memorandum of Agreement with the Alfred

Project Number	CF15/2424 - 2015000975
Project Title	An epidemiological study of rapid sequence intubation in out-of-hospital non-traumatic brain injuries
Chief Investigator	Dr Paul Jennings
Valid until	16 June 2020

Notes:

1. Registration is valid whilst you hold a position at Monash University and approval at the primary HREC is current.
2. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
3. **End of project:** Notification should be provided at the conclusion of the project. MUHREC should also be notified if the project is discontinued before the expected date of completion.
4. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to the project in accordance with The *Australian Code for the Responsible Conduct of Research*.

Professor Nip Thomson
Chair, MUHREC

Cc: Mr Peiter Fouche; Dr Malcolm Boyle

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ABN 12 377 614 012 CRICOS Provider #00008C

Appendix B: Monash University Human Research Ethics Committee approval certificate for Chapters 3 to 6

Monash University Human Research Ethics Committee

Approval Certificate

This is to certify that the project below was considered by the Monash University Human Research Ethics Committee. The Committee was satisfied that the proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research* and has granted approval.

Project Number: 8618
Project Title: Stroke RSI
Chief Investigator: Dr Paul Jennings
Expiry Date: 06/06/2022

Terms of approval - failure to comply with the terms below is in breach of your approval and the *Australian Code for the Responsible Conduct of Research*.

1. The Chief Investigator is responsible for ensuring that permission letters are obtained, if relevant, before any data collection can occur at the specified organisation.
2. Approval is only valid whilst you hold a position at Monash University.
3. It is responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash letterhead and the Monash University complaints clause must include your project number.
6. Amendments to approved projects including changes to personnel must not commence without written approval from MHUREC.
7. Annual Report - continued approval of this project is dependent on the submission of an Annual Report.
8. Final Report - should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected completion date.
9. Monitoring - project may be subject to an audit or any other form of monitoring by MUHREC at any time.
10. Retention and storage of data - The Chief Investigator is responsible for the storage and retention of the original data pertaining to the project for a minimum period of five years.

Thank you for your assistance.

Professor Nip Thomson

Chair, MUHREC

CC: Adj Prof Stephen Bernard, Dr Karen Smith, Dr Malcolm Boyle

List of approved documents:

Document Type	File Name	Date	Version
Supporting Documentation	RSI in stroke proposal v4	26/05/2017	4

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Appendix C: Supplementary materials

C.1.1 Study characteristics, prevalence of NTBP, Newcastle Ottawa scale, search terms, quality checklist and quality guideline for chapter 2

Table S1 Study characteristics

Study (year)	Prevalence Bias score (category)	non-traumatic brain pathologies type	Practioner	Type of ETI	Location of ETI	Prevalence (%)	Intubation survival (%)	Non-intubation survival (%)
Alldredge 1995	3.5 (high)	seizures	paramedic	NR	out-of-hospital	16/38 (42)	NR	NR
Bernard 2015	4 (mod)	mixed non-traumatic brain pathologies	paramedic	RSI	out-of-hospital	551/551 (100)	NR	NR
Braun 2017	4.5 (mod)	seizures	NR	NR	ED	23/44 (52)	NR	NR
Chamberlain 1997	2.5 (high)	seizures	NR	NR	ED	2/24 (8)	NR	NR
Chiulli 1991	2.5 (high)	seizures	NR	NR	ED	17/38 (45)	NR	NR
Dieckmann 1994	3.5 (high)	seizures	phys/para	NR	ED	12/31 (39)	NR	NR
Elmer 2013	5 (mod)	h/stroke	NR	NR	pre/ED	557/697 (80)	NR	NR
Emerman 1987	3.5 (high)	toxicity	NR	NR	ED	37/92 (40)	NR	NR
Fletcher 2013	4 (mod)	seizures	NR	NR	ED	40/193 (21)	NR	NR
Fouche 2017	5 (mod)	mixed non-traumatic brain pathologies	paramedic	RSI	out-of-hospital	1940/1940 (100)	771/1112 (69)	NR
Galustyan 2003	4 (mod)	seizures	phys/para	NR	pre/ED	104/1516 (7)	NR	NR
Holsti 2007	4 (mod)	seizures	phys/para	NR	pre/ED	11/57 (19)	NR	NR
Katz 2017	2.5 (high)	toxicity	NR	NR	ED	9/11 (82)	8/9 (89)	2/2 (100)
Kohli 2008	3 (high)	toxicity	NR	NR	ED	3/11 (27)	3/3 (100)	108/108 (100)
Langer 2014	3.5 (high)	seizures	NR	NR	ED	75/170 (44)	NR	NR
Lee 2016	5 (mod)	toxicity	NR	NR	ED	23/45 (51)	NR	NR
Lewena 2006	4 (mod)	seizures	NR	RSI	ED	26/37 (70)	NR	NR
Lewena 2009	4.5 (mod)	seizures	NR	RSI	ED	134/467 (29)	NR	NR
Li 1998	5.5 (mod)	toxicity	physician	NR	ED	4/7 (57)	NR	NR
Meyer 2000	4 (mod)	h/stroke	physician	RSI	out-of-hospital	11/20 (55)	NR	NR
Nass 2017	5.5 (mod)	seizures	NR	NR	ED	4/223 (2)	NR	NR
Nielsen 2012	3 (high)	mixed non-traumatic brain pathologies	physician	NR	out-of-hospital	17/67 (25)	NR	NR
Orr 1991	4.5 (mod)	seizures	NR	NR	ED	32/54	NR	NR
Pakkanen 2015	5 (mod)	mixed non-traumatic brain pathologies	physician	NR	out-of-hospital	214/214 (100)	140/214 (65)	NR
Perry 1998	5 (mod)	toxicity	phys/para	NR	pre/ED	9/14 (64)	9/9 (100)	5/5 (100)
Petchy 2014	5.5 (mod)	i/stroke	physician	NR	pre/ED	326/8600 (4)	5/31 (16)	NR
Phillips 1997	5.5 (mod)	toxicity	physician	NR	ED	57/140 (41)	NR	NR
Saber 2016	6 (mod)	i/stroke	NR	NR	ED	157/615 (26)	NR	NR
Santoli 2001	3.5 (high)	i/stroke	physician	NR	ED	65/277 (23)	16/58 (28)	NR
Sato 2017	4.5 (mod)	seizures	physician	NR	ED	59/822 (7)	NR	NR
Shaner 1998	5 (mod)	seizures	physician	NR	ED	12/36 (33)	NR	NR
Silbergleit 2012	6.5 (mod)	seizures	phys/para	NR	pre/ED	127/893 (14)	NR	NR
Stromberg 2015	4.5 (mod)	toxicity	NR	NR	ED	6/9 (67)	NR	NR
Syverud 1988	6 (mod)	mixed non-traumatic brain	phys/para	RSI	out-of-hospital	11/11 (100)	NR	NR

		pathologies						
Theodosiou 2011	4 (mod)	mixed stroke	NR	RSI	ED	51/51 (100)	8/51 (16)	NR
Tobochnik 2015	3.5 (high)	seizures	NR	NR	ED	117/247 (47)	NR	NR
Uda 2017	4 (mod)	seizures	NR	NR	ED	16/99 (16)	NR	NR
Unverir 2006	4.5 (mod)	toxicity	NR	NR	ED	34/356 (10)	NR	NR
Vicario 1986	3.5 (high)	encephalopathy	physician	NR	ED	26/39 (67)	18/26 (69)	13/13 (100)
Vilke 2002	4.5 (mod)	seizures	NR	NR	ED	7/86 (81)	NR	NR
Vohra 2015	6 (mod)	seizures	phys/para	NR	pre/ED	218/1023 (21)	202/218 (93)	802/805 (99.6)
Wang 2011	3 (high)	mixed non-traumatic brain pathologies	paramedic	mix	out-of-hospital	765/765 (100)	NR	NR
Warden 2006	4.5 (mod)	seizures	NR	NR	pre/ED	12/58 (21)	NR	NR
Yilmaz 2017	5 (mod)	toxicity	NR	NR	ED	5/30 (17)	NR	NR
Yock-Corrales 2016	5 (mod)	mixed stroke	NR	NR	ED	20/64 (31)	NR	NR
Zuckerbraun 2006	4 (mod)	seizures	physician	RSI	ED	21/21 (100)	NR	NR

NR =not reported; RSI = rapid sequence intubation ; ED = emergency department; phys/para = physician paramedic; h/stroke = hemorrhagic stroke; i/stroke = ischemic stroke; pre/ED = out-of-hospital and ED; mod = moderate

Table S2 Prevalence of intubation in non-traumatic brain pathologies by subgroup, quality effects model

Study or subgroup	Proportion	LCI 95%	HCI 95%	Weight (%)
Seizures				
Shaner 1988	0.33	0.19	0.50	0.78
Orr 1991	0.59	0.46	0.72	0.77
Chiulli 1991	0.45	0.29	0.61	0.39
Dieckmann 1994	0.39	0.22	0.57	0.53
Alldredge 1995	0.42	0.27	0.58	0.55
Chamberlain 1997	0.08	0.00	0.24	0.36
Vilke 2002	0.08	0.03	0.15	0.90
Galustyan 2003	0.07	0.06	0.08	5.86
Warden 2006	0.21	0.11	0.32	0.79
Lewena 2006	0.70	0.54	0.84	0.62
Holsti 2007	0.19	0.10	0.31	0.69
Lewena 2009	0.29	0.25	0.33	2.42
Silbergleit 2012	0.14	0.12	0.17	5.94
Fletcher 2013	0.21	0.15	0.27	1.18
Langer 2104	0.44	0.37	0.52	0.96
Tobochnick 2015	0.47	0.41	0.54	1.20
Vohra 2015	0.21	0.19	0.24	6.18
Braun 2017	0.52	0.37	0.67	0.73
Nass 2017	0.02	0.00	0.04	1.76
Sato 2017	0.07	0.06	0.09	3.83
Uda 2017	0.16	0.09	0.24	0.84
Seizures subgroup	0.18	0.10	0.27	37.27

Encephalopathy				
Vicario 1986	0.67	0.51	0.81	0.55
Encephalopathy subgroup	0.66	0.51	0.81	0.55
Mixed stroke				
Yock-Corrales 2016	0.31	0.20	0.43	0.90
Mixed stroke subgroup	0.32	0.20	0.43	0.90
Haemorrhagic stroke				
Meyer 2000	0.55	0.33	0.76	0.56
Elmer 2013	0.80	0.77	0.83	3.70
Hemorrhagic stroke subgroup	0.79	0.47	1.00	4.27
Ischemic stroke				
Santoli 2001	0.23	0.19	0.29	1.29
Petchy 2014	0.04	0.03	0.04	42.57
Saber 2016	0.26	0.22	0.29	4.01
Ischemic stroke subgroup	0.06	0.00	0.32	47.87
Mixed non-traumatic brain pathologies				
Nielsen 2012	0.25	0.16	0.37	0.55
Mixed non-traumatic brain pathologies subgroup	0.26	0.16	0.37	0.55
Toxicity and toxic encephalopathy				
Emerman 1987	0.40	0.30	0.50	0.72
Phillips 1997	0.41	0.33	0.49	1.36
Li 1998	0.57	0.19	0.92	0.71
Perry 1998	0.64	0.37	0.88	0.68
Unverir 2006	0.10	0.07	0.13	1.97
Kohli 2008	0.03	0.00	0.07	0.66
Stromberg 2015	0.67	0.32	0.94	0.59
Katz 2016	0.82	0.53	0.99	0.33
Lee 2016	0.51	0.36	0.66	0.82
Yilmaz 2017	0.17	0.05	0.32	0.75
Toxicity subgroup	0.25	0.06	0.48	8.59
Pooled	0.12	0.01	0.33	100.00
I^2	98.9	98.8	99.1	
Cochran's Q	*3610.2*			
Chi^2, p	*<0.001*			
Q-Index	*20.7*			

LCI = lower confidence interval; HCI = higher confidence interval

Table S3 Newcastle-Ottawa scale for cohort studies, intubation versus no-ETI

Author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Quality
Vohra 2015		*	*	*		*	*	*	Poor
Vicario 1986	*	*	*	*				*	Poor
Perry 1998		*	*	*		*	*	*	Poor
Katz 2016	*	*	*	*		*	*	*	Poor
Kohli 2008		*	*	*		*	*	*	Poor

* Indicates a star, which shows that item is relatively unbiased. Blank space is no-star, indicating high risk of bias.

Appendix 1

Medline search terms

1. rapid sequence intubation .mp.

2. rapid sequence intubation .tw.

3. rapid seq$.tw.

4. rapid sequence induction.mp.

5. rapid-seq$.tw.

6. RSI.tw.

7. rapid-sequence-intub$.tw.

8.heatstroke.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

9.stroke.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

10.seizures.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

11.brain tumour.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

12.meningitis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

13.encephalitis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

14.intracranial haemorrhage.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

15.brain neoplasms.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

16.hypoxic brain damage.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

17.Wernickes encephalopathy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

18.heatstroke.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

19.hydrocephalus.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

20.non traumatic brain injury.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

21.brain tumour.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

22.meningitis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

23.encephalitis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

24.intracranial haemorrhage.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

25. Ntraumatic brain injury .tw.

26. non traumatic brain injury.mp.

27. non-traumatic brain injury.tw.

28. non traumatic brain$.tw.

29. non traumatic coma.tw.

30.endotracheal intubation .mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

31. endotracheal intubation .tw.

32. intubation .tw.

33. ETI.tw.

34. tracheal intubation .tw.

35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 30 or 31 or 32 or33 or 34

36.8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

37. 35 and 36

38. limit 37 to (english language and humans)

Embase and Central search terms

1. rapid sequence intubation .mp.

7

2. rapid sequence intubation .tw.

3. rapid seq$.tw.

4. rapid sequence induction.tw.

5. rapid-seq$.tw.

6. RSI.tw.

7. rapid-sequence-intub$.tw.

8. heatstroke$.tw.

9. stroke.tw.

10. seizure$.tw.

11. brain tumour.tw.

12. meningitis.tw.

13. encephalitis.tw.

14. intracranial haemorrhage.tw.

15. brain neoplasm$.tw.

16. hypoxic brain$.tw.

17. Wernicke$.tw.

18. heatstroke.tw.

19. hydrocephal$.tw.

20. non traumatic brain injury.tw.

21. brain tumou$.tw.

22. Ntraumatic brain injury .tw.

23. non traumatic brain$.tw.

24. non traumatic coma.tw.

25. endotracheal intubation .tw.

26. intubation .tw.

27. ETI.tw.

28. tracheal intubation .tw.

29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 25 or 26 or 27 or 28

30. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

31. 29 and 30

32. limit 31 to (human and english language)

Appendix 2

QUALITY CHECKLIST FOR A SYSTEMATIC REVIEW OF EMERGENCY INTUBATION IN NON-TRAUMATIC BRAIN PATHOLOGIES

HOW TO USE THIS CHECKLIST

1. Carefully read all articles, and reread the relevant portions with the checklist, systematically considering each category on the list.
2. Answers are scored *high risk* or *low risk*, based on the criteria in the table below.
3. After each item of the list has received ether a *high risk* or *low risk* rating, the study then receives an overall rating by adding the number of low risk scores for item nine (Summary item on the overall risk of study bias).

ITEMS
1. Does the emergency department (ED) or emergency service (EMS) treat patients with non-traumatic brain pathologies (non-traumatic brain pathologies) that are similar to the patients that the study results will be generalized? The population being served had to be adults and children of all ages and consist of a typical mix of illness severity. • Yes (LOW RISK): The EMS/ED patient population was a close representation of the typical non-traumatic brain pathologies population. • No (HIGH RISK): The EMS/ED patient population was not a close representation of the typical non-traumatic brain pathologies population, or not reported sufficiently.
2. Was the defined sampling frame (from which the sample was drawn) made up of all data collected by the emergency service or ED? • Yes (LOW RISK): the defined sampling frame of the study consists of all records of the study period, no data restriction to a subgroup. • No (HIGH RISK): Data was restricted and the defined sampling frame of the study did not consist of all records, or not

reported sufficiently.
3. Was some form of random selection used to select the sample from the defined sampling frame, or did the researchers endeavor to access all records (a census)? • Yes (LOW RISK): A census or random sample was used. • No (HIGH RISK): The sample was not randomly selected or census used, it was selected by handpicking etc., or not reported sufficiently.
4. Was the non-response bias (non-availability of data after selection to the sample) less than 20%? After the researcher selected cases for inclusion, did they obtain data from most of the selected subjects? • Yes (LOW RISK): The sample had better than or equal to 80% availability of data. • No (HIGH RISK): the sample is less than 80% of the cases that should have been included, or not reported sufficiently.
5. Was acceptable non-traumatic brain pathologies definitions used when such definitions were required? That is, were the terms and definitions used devoid of any ambiguity? • Yes (LOW RISK): non-traumatic brain pathologies definitions had acceptable definitions, or lacked ambiguity. • No (HIGH RISK): non-traumatic brain pathologies definitions are acceptable and not ambiguous.
6. Were any reasonable steps taken to ensure accuracy of the intubation success and non-traumatic brain pathologies prevalence statistics? Endotracheal success must be verified by reliable means such as radiography and successful intubation proportion by clinical means and by using appropriate technology such as $ETCO_2$. non-traumatic brain pathologies presence needs to be verified by acceptable clinical means. • Yes (LOW RISK): Statistics were reliable, appropriate verification was used. • No (HIGH RISK): Statistics were unreliable, appropriate verification was not used or not reported sufficiently.
7. Did the numerator(s) and denominator(s) for the non-traumatic brain pathologies intubation fraction translate to the reported statistic (proportion)? If a study reports an intubation proportion in their non-traumatic brain pathologies cohort, and also reports the fraction/ratio that the percentage is derived from, check that they match. • Yes (LOW RISK): Numerator and denominator are correct; they match the reported statistic. • No (HIGH RISK): Numerator and denominator are incorrect; they do not match the reported statistic or statistic is reported without evidence of how it was derived, or not reported sufficiently.
8. Was the mode (e.g. healthcare records, clinician interviews etc.) of data collection the same for all subjects? • Yes (LOW RISK): All data was collected in the same way. • No (HIGH RISK): Some of the data was collected in different ways, or not reported sufficiently.

9. Sum the number of low risk scores and add this to item nine. Sum the number of low risk scores and add this to item nine. Classify scores into categories: 1,2,3 = high risk of bias 4,5,6 = moderate risk of bias 7,8 = low risk of bias

Appendix 3

Guidelines for using the intubation in non-traumatic brain pathologies checklist

This guideline aims to assist the rater in the interpretation of the checklist, and provides examples. To start, some definitions plus examples:

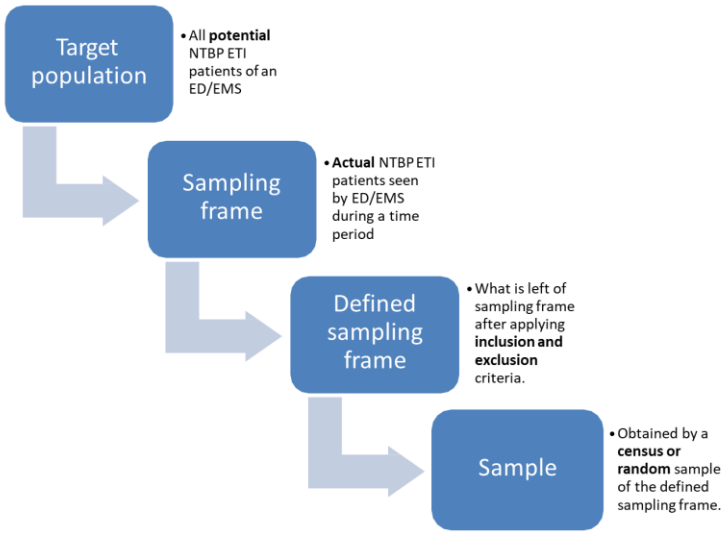
Target population - The target population refers to the group of people to which the results of the particular study will be generalised. This is the population from which the particular emergency service or emergency department (ED) obtains its patients. It might be all potential non-traumatic brain pathologies patients that could potentially receive intubation in a specific geographical area (such as a state, province, city) served by a particular emergency service or ED. Example: an ambulance service such as Ambulance Victoria in Australia is serves all potential non-traumatic brain pathologies patients in the state of Victoria, Australia. The target population is therefore the non-traumatic brain pathologies that could receive intubation over the whole of Victoria. Another example, an ED such as The Alfred Hospital has a target population of all non-traumatic brain pathologies of whoever is eligible for admission to the ED with a non-traumatic brain pathologies in the catchment area of that hospital (which is harder to define).

Sampling frame - The sampling frame is a list of the patients attended to in the ED or by the EMS for a particular period of time. The study sample is drawn from this list. Examples: All drug overdose patients treated by paramedics in Victoria, or all ED patients with seizures admitted to that ED for the study period.

Defined sampling frame- After the researchers apply the particular studies inclusion and exclusion criteria to sampling frame, they are left with the *defined sampling frame.* Ideally the inclusion and exclusion criteria are such that the defined sampling frame resembles the sampling frame closely, but this is often not the case. Example: A study has defined sampling frame only paediatric patients (excluding adults) with stroke treated by paramedics for 12 months in Victoria.

Sample- The *sample* is the group of patients extracted out of the defined sampling frame for inclusion in the study.

Figure 2 Study sample selection process for a typical study



Item one

This item aims to assess the extent that the composition of the *target population* affects external validity of a study. An externally valid study meant that the results of the study can be readily applied to a group of patients typically seen in practice. Item one does this by finding out if the patient the particular service or ED treats is similar to the "wider" population of non-traumatic brain pathologies patient to which the results of this review will be extrapolated. In the context of endotracheal intubation (ETI) in non-traumatic brain pathologies, a typical target population is one comprised of a mix of all ages and with non-traumatic brain pathologies and with a typical illness severity. Typical illness severity is defined here as a patient population that normally includes at least five percent severely ill non-traumatic brain pathologies patients. Severely ill patient are those that are usually unconscious/comatose at the time of RSI, or have an illness severity score that indicates severe illness or unconsciousness. Illness severity score include (but are not limited to):

Glasgow Coma Scale, Charlson; Age-combined Charlson Co-morbidity Index or ACCI; Deyo; Quan ; Romano; Elixhauser; D'Hoore ; Ghali ; comorbidity ; case mix or case-mix; empirical weights; Pittsburgh Cardiac Arrest Category or PCAC; Therapeutic Interventions Scoring System or TISS; Acute Physiology Age and Chronic Health Evaluation Systems or APACHE or APACHE II or APACHE III; Simplified Acute Physiology Score or SAPS; Mortality Prediction Models or MPM; Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity or POSSUM; Sequential Organ Failure Assessment or SOFA; Comorbidity-Polypharmacy Score or CPS; Diagnosis-related group or DRG; Healthcare Resource Groups or HRG; Pediatric Risk of Mortality or PRM; Pediatric Index of Mortality or PIM; Good Outcome Following Attempted Resuscitation or GO-FAR; OHCA score; Full Outline

of unresponsiveness or FOUR; Cardiac Arrest Survival Post-Resuscitation In-hospital or CASPRI; index of co-existent diseases or ICED; Wright-Khan indices; Chronic Disease Score.

It might be that the service treats patients that are typical (all ages and of typical illness severity) but the researchers select only a subset (such as paediatric) for their study. In this instance item one will still receive a low risk of bias score, because this service treats a "typical" population and the reduction to paediatric-only for their study will be assessed in another item of this checklist. Therefore, item ones ask: whom with non-traumatic brain pathologies does this service or ED typically treat, and are they comparable to the non-traumatic brain pathologies super-population that we are going to generalize the systematic review results to? **Note that this item is concerned with the composition of the *patient population* the emergency service or ED typically sees, not of the *sample* or the *sampling frame***. Make an inference of the service or ED target population from the study sample and descriptions in the methods section.

Examples	Rating and comments
A study on strokes in an ED that typically treat strokes of all ages, and at least 52% of their strokes have a GCS ≤ 9 or NIHSS ≥ 16	Yes (LOW RISK). This ED normally treats patients that are of all sex and ages, and an acceptable proportion of their target population has severe illness (this can be inferred from the study cohort)
A paramedic service treats patients of all ages, race and illness severity, however, their service is to cities and other major metropolitan areas, no rural patients included.	Yes (LOW RISK). All criteria are met; if service is in a city this does not affect the mix for our purposes.
A specialised EMS stroke service transports only strokes that have an initial GCS of ≤ 9 and or NIHSS ≥ 16 that are adults.	No (HIGH RISK). This EMS does not treat patients that are comparable to the "typical" EMS, and the results of a study using this data will not be easily generalizable.
A road based service does not report the composition of their usual seizure patient population. However, their study sample contains 19% with status epilepticus of all ages.	Yes (LOW RISK). Although this study does not report any illness severity scores, those with status epilepticus are comatose upon treatment and are obviously severely ill. It is evident that they don't only treat severely ill or only mild or moderately ill seizures, they treat the whole range of severity.
An ED based study does not report the nature of their serviced population, no mention of illness severity but they do report age range. Nor can illness severity distribution be	No (HIGH RISK). We need to know that some of the patients this ED treats that are typically severely ill and also we need to know the ages.

reasonably inferred from the text.	

Item two

If the records collected by the researchers are not the whole *sampling frame* by choice of the researchers – i.e. only a part of the records from the *sampling frame* form their reduced cohort due to investigator restrictions, then we have a high risk for bias. For example, if an ED typically treats all types of stroke, all ages with many of them critically ill, but the researchers exclude ischemic strokes patients from this *sampling frame,* resulting in a *defined sampling frame* without ischemic strokes patients. This is an instance of high risk of bias, since their research population is only a subset of the actual group of patients seen by that service. Please note data "restriction" can happen without investigator choices - for example if a subgroup of data is not available for whatever reason (e.g. data lost in a fire). This is assessed by item four; the focus of item two is data restriction by the study investigators.

Examples	Rating and comments
A helicopter service has a typical seizure population of all illness severity types, all ages in a large metro area. Researchers set out to measure intubation proportions in seizures in a subset of children only.	No (HIGH RISK). The sampling frame is restricted to a subgroup (children) by their inclusion criteria, making the results less useful to this systematic review.
An ED decides to find out the survival after intubation of all alcohol overdose patients they treat for ten years. The *sampling frame* is not restricted as they identify all overdose patients that received intubation from healthcare records.	Yes (LOW RISK). There was no restriction of data they collected from the whole sampling frame.
A paediatric road based EMS service aims to identify survival after intubation in their paediatric population. Their sampling frame is all records in their service without restriction. However, they could only get records for 68% of the children.	Yes (LOW RISK). There were no subgroups. The fact that they could get only 68% of records did not matter for this item; it is assessed in item four.
An ED encephalopathy intubation study states in its criteria that it excludes cases with contraindications to Suxamethonium and Ketamine, which are their usual RSI drugs.	Yes (LOW RISK). Excluding Patients with contraindications to intubation drugs is not data restriction, as they would not have received intubation anyway.

A study aims to find the proportion of strokes that receive intubation in an ED. This ED treats all non-traumatic brain pathologies types, but they only want to focus on strokes, and only strokes are included in their study.	Yes (LOW RISK). The aim of this systematic review is to study the various non-traumatic brain pathologies separately also. Very few studies will report all non-traumatic brain pathologies together, and almost all will study non-traumatic brain pathologies separately. For example, a study might only focus on strokes; another study will focus on seizures. This is not data restriction (for our purposes).
A study does not report how they derived their sampling frame and we do not know if data restriction exists.	No (HIGH RISK). How do we know the sampling frame matches the target population closely?

Item three

The study sample should closely resemble the *defined sampling frame*. See definitions above, the *sampling frame* and *defined sampling frame* are not quite the same. Sampling can be done with a census or a random sampling. A census is when the researcher aims to collect every healthcare records/clinical sheet/data items of their defined sampling frame. A random sample is done by using a random process to select a representative sample from the *defined sampling frame*. A random sample should be large enough to achieve a representative sample. Unlike item two, which determines how data was restricted; this item focuses on whether the study sample was created in a way that all records of the defined sampling frame had an equal chance of being included.

Examples	Rating and comments
A paramedic organization aims to find the intubation proportion of recreational drug overdoses. They decide to include only male patients, no females. Furthermore, they decide to do a random sample of this patient population that includes only males.	Yes (LOW RISK). Regardless of the data restriction to males only (assessed by item two), researchers did a random sample. The scores of item one and two do not impact on this item.
A paediatric ED aims to find the proportion of intubation s of non-traumatic hydrocephalus over a year. Although they had access to all records, they decided to use only the records of intubation by anaesthesiologists and emergency physicians as the *defined sampling*	Yes (LOW RISK). They took a census of their defined sampling frame. Similarly to above and regardless of the data restriction, the scores of item one and two do not impact on this item.

frame **(and they state this in their criteria) and undertook a census this select group.**	
An aeromedical nurse-based service aims to assess the intubation survival of all patients with non-traumatic coma. They access all records over a year, and included these in their study.	Yes (LOW RISK). This is an example of a census.
An ED wants to find the proportion and survival hazard rate of intubation after suicides due to poisoning for one year. They identify that 23% of the records are in hardcopy (not electronic) and they don't go to the trouble of obtaining these records due to the extra labour it entails.	No (HIGH RISK). They did not use a random process or census to select the sample; they handpicked records that are easily obtainable despite all records available.

Item four

If the sample is much smaller due to non-availability of data (not by investigator choice as in item two) then we cannot be sure that the results of the study are true. This is because the non-available data might be systematically different from the available data, causing a non-response bias. Data should be available to equal or more than 80% of cases identified after census or random selection of the *defined sampling frame*. Stated differently**, if the researcher is unable to obtain data from ≥80% of cases that were selected into the study (e.g. through ID numbers), then this poses a significant risk of non-response bias.** Or if they got data for less than 80%, but show in an analysis that found no difference in important variables (e.g. age, illness severity etc.) between responders and non-responders then response bias is not a problem. Conversely, if they have more than 80% but an analysis show differences, bias is then likely. If it is not clear from the study, i.e. it cannot be assessed due to lack of information, and then this too poses a high risk of bias. Please note that this item is different from item two, which assesses *data restriction* to a subgroup, which is typically done using the inclusion/exclusion criteria. If no information is available to assess non-response bias, then we must assume high risk.

Examples	Rating and comments
An intubation after heatstroke study identified 350 records that met inclusion and exclusion criteria; but they used 212 records because outcomes or intubation success information were incomplete for the rest of the sampling	No (HIGH RISK).Non-response is 100-(212/350) = 39%, which is larger than 20%.

frame.	
An ED based study reports that they could not get intubation success data for 29% of the stroke records they identified. Nonetheless they show with a statistical analysis that the missing data was not significantly different from the non-missing dataset.	Yes (LOW RISK). Although they have only the data for less than 80% of patients, they do show that the missingness is not a problem.
A study reports that the sample size is 456 stroke patients, but they do not mention how this sample was selected and if this was a sample after non-response.	No (HIGH RISK). We are unable to assess non-response bias, as the authors did not mention how large the *defined sampling frame* was from which the 456 were drawn. Perhaps the sampling frame had 1000 patients, and they got only 456!

Item five

To find a truthful (unbiased) prevalence of intubation in a cohort of non-traumatic brain pathologies an acceptable definition of non-traumatic brain pathologies is important. The prevalence might vary depending on the definitions used for non-traumatic brain pathologies. If no acceptable definition for the particular non-traumatic brain pathologies is found a high risk of bias assumption must be made. Acceptable definitions for non-traumatic brain pathologies include referenced sentences that are adequate to the rater, or a list of codes (such as ICD10) that define the non-traumatic brain pathologies type. For this item we are concerned with definitions, not methods of diagnosis, which will be assessed in item six.

Examples	Rating and comments
An ED study reports intubation of 23%, of their strokes. Stokes is defined by a list of ICD10 codes.	Yes (LOW RISK). They define strokes using an acceptable method, and the ICD10 codes are themselves sensible stroke codes. If their codes include illnesses that are not stroke, then this would not meet the criteria for an adequate definition.
An out-of-hospital study aims to find the proportion of RSI and survival in strokes and seizures. They give definition from a recent well cited paper for both haemorrhagic and ischemic strokes, but include TIA in their definition and make a solid argument for the inclusion of TIA	Yes (LOW RISK). Although including TIA in their stoke definition is unusual they make an acceptable case for it. For this review it does not matter that they defined successful intubation well, since most papers define intubation success in terms of verification, which is assessed by the next item.

in their stokes. Also, they define successful RSI as "Successful intubation was defined as the placement of endotracheal tube in the trachea beyond the vocal cords and confirmed by clinical means and/or end-tidal CO2 waveform".	
A study reports survival and intubation proportions of seizures. They do not mention anywhere in the paper what they consider a seizure.	No (HIGH RISK). They need to define seizures; they defined nothing! Defining the non-traumatic brain pathologies is important, since some definitions of non-traumatic brain pathologies are less obvious and more complicated than seizures, such as strokes (see above example), hydrocephalus, brain damage due to toxicity, metabolic conditions, alcohol and drug overdose and anoxia.

Item six

The aim of this review is to count the prevalence of intubation in non-traumatic brain pathologies. We therefore need to know that **both** intubation and is correctly verified and that is correctly diagnosed.

Firstly, to calculate the prevalence of intubation in non-traumatic brain pathologies, we will count only *successful* ETI. intubation success needs to be verified to be trustworthy. Intubation success is independently verified by radiological means or confirmation by another clinician by visual inspection of the endotracheal tube having passed through the vocal cords, or by the use of technology such as end-tidal CO_2, colorometric CO_2 bulb/syringe devices (or any other similar technology). By "confirmation by another clinician by visual inspection" it is meant that another clinician visually inspects (with a laryngoscope, for example) the airway after the intubation to verify placement. This commonly happens when a clinician hands over an intubated patient to the Emergency Department where the ED physician confirms placement by inspecting the airway with a laryngoscope or ETCO2 monitor and auscultation etc. It he paper indicates that another clinician verified ET placement, regardless of how that clinician verified, then this is acceptable. But clinician verification is just one acceptable way of confirmation. intubation success can also be verified independently by other means such an x-ray (radiological) or colorometric CO_2 detectors or bulb/syringe devices or any other acceptable technology. You are the judge of "acceptable technology". Please not that these other means (radiological, $ETCO_2$, bulb devices etc.) do not require another clinician double-checking them, for example an x-ray does not have to be read by two clinicians, nor does a bulb/syringe device need double verification. Independent verification is not foolproof; but our aim is to be reasonably sure of the veracity of RSI events.

Secondly, non-traumatic brain pathologies need to be diagnosed by reliable methods. The study must mention how they diagnosed the non-traumatic brain pathologies, and this must be by methods judged to be acceptable

by the rater. Usually this is based on radiological means such as MRI, CT-scan, X-ray etc. or by clinical means. Surgical verification or other acceptable methods are fine too. Ultimately diagnostic /verification methods will vary greatly across geographical regions. The rater should judge if the method is acceptable or not considering the context of the particular study.

Examples	Rating and comments
An intubation study on tricyclic overdoses from a ground based EMS service reports intubation proportions. They state that tricyclic overdose was confirmed by toxilogical screening, but they do not say how intubation success was verified.	No (HIGH RISK). They do verify the type of non-traumatic brain pathologies well, but not the intubation success. They need acceptable verification of both these, not just half.
An ED study on meningitis RSI proportions state that meningitis was confirmed by MRI and clinical means, and also state that intubation success was confirmed by clinical means and the use of a bulb devise plus confirmation by a second clinician inspecting the trachea with a scope and x-ray	Yes (LOW RISK). Both the non-traumatic brain pathologies (meningitis) and intubation success was verified.

Item seven

intubation proportions reported for non-traumatic brain pathologies must match the fraction reported from which the proportion is derived. Often this supporting information is located in a table, or as free text in the results section. It is rather tedious to double check the papers calculations, but please be thorough. Please note that you do not have to check the proportions for statistics that are not of interest to us for this review. We only check the proportion of successful intubation in the non-traumatic brain pathologies cohort. Often papers report outcomes and statistics that are not relevant to this systematic review; we are not concerned with the veracity of these statistics. For this review we only extract and analyse the proportion of non-traumatic brain pathologies that had received successful ETI. We do not check that the survival fractions are correct, we will not meta-analyse these (there are too few).

Examples	Rating and comments
A intubation study on seizures in a helicopter service report 23% ETI, and in table one we find the numerator and denominator that was used to derive this 23% figure. The fraction from the	No (HIGH RISK). 70/450 = 16%, not 23%, they miscalculated.

table is 70/450.	
An ED based study report intubation proportion of 18% with a fraction in table one 49/270 and survival for the intubation group of 40% = 20/49. They also report fractions and statistics for oesophageal intubation and hyperventilation.	Yes (LOW RISK). The statistic for intubation proportion has a supporting fraction that is correct. Esophageal intubation , survival and hyperventilation statistics are not relevant to us, don't check these.
A study reports intubation proportion in hydrocephalus of 18% with no supporting fractions anywhere in the paper.	No (HIGH RISK). We need to verify that they calculated correctly, but there are no supporting fractions to be reported.

Item eight

Some methods of data collection are more reliable than others. A study should use uniform methods of collection all of its data. If they used more than one method, then one part of the study has data that is less reliable then the other. If they do not provide any information on how data was collected a high risk to bias results.

Examples	Rating and comments
A study collects 60% of its data from healthcare records, and the other 40% from a mix of video footage and printouts from machines plus post event debrief and documentation.	No (HIGH RISK). Multiple methods of data collection were used here.
A study collects 98% of its data from electronic healthcare records, and the other 2% from a hand written records	No (HIGH RISK). Multiple methods of data collection were used here, although only for a small proportion, it is still a problem for the purposes of this review.
A study does no stipulate how data was collected	No (HIGH RISK). We cannot assume that data collection was uniform.

Item nine

See quality checklist for explanation on how to calculate summary score.

Table C1.2: Multivariable Logistic Regression of Prehospital Predictors of Survival-to-hospital Discharge for RSI in all NTBP

Factor	Adjusted OR (95% CI)	*P*-value
Age (years)	0.95 (0.94–0.97)	< 0.001
Anoxic brain injury	0.19 (0.07–0.55)	0.001
Elixhauser–Walraven score†		< 0.001
5	1.00 (ref)	
10	0.002 (0.001–0.09)	
20	0.01 (0.001–0.22)	
30	0.02 (0.001–0.24)	
40	0.003 (0.001–0.11)	
Final pulse rate (p/min)	0.99 (0.98–0.99)	0.008
Haemorrhagic stroke (yes)	0.32 (0.19–0.54)	< 0.001
ICU stay	1.68 (1.06–2.69)	0.03
Initial pulse rate (p/min)††		0.002
40	0.94 (0.90–0.98)	
60	1.00 (ref)	
70	1.05 (1.02–1.08)	
100	1.37 (1.12–1.67)	
150	3.59 (1.60–8.07)	
Maximum blood sugar level (mmol/l)		0.04
1.2–4.99	0.23 (0.09–0.61)	
5–9.99	1.0 (ref)	
10–14.99	1.16 (0.68–1.96)	
15–19.99	1.59 (0.61–4.15)	
≥ 20	1.23 (0.25–5.97)	
GCS$	1.11 (1.04–1.18)	0.001
Seizures	15.18 (7.53–30.6)	< 0.001
Toxicity and toxic encephalopathy	25.47 (9.78–66.3)	< 0.001
Other encephalopathy types	0.10 (0.03–0.30)	< 0.001

† Elixhauser score fitted as fractional polynomial terms: β_1 (Elixhauser + 1/10)^3 + β_2 (Elixhauser + 1/10)^{3}ln + β_3 (Elixhauser + 1/10)^{3}ln^2 + β_4 (Elixhauser + 1/10)^{3}ln^3

†† Initial pulse rate fitted as a fractional polynomial term: β_1 (Initial pulse rate + 1/10)^3

$ Highest GCS measured by paramedics on scene. Variables included in multivariable were only those that were significant at the 5% level. *(OR) odd ratio

Table C1.3 to 5: Estimates of logistic regression of RSI adjusted for covariates in brain trauma and strokes

Table S1A Estimates of a logistic regression model of RSI adjusted for covariates in 42,437 traumatic brain injuries

Factor	Adjusted OR (95% CI)	P-value
Age (years)*		
40	1.00 (ref)	
60	0.96 (0.97 to 0.97)	<0.001
80	0.91 (0.90 to 0.92)	<0.001
Elixhauser-Walraven score†		
10	1.00 (ref)	
20	0.67 (0.62 to 0.72)	<0.001
30	0.34 (0.28 to 0.41)	<0.001
40	0.14 (0.10 to 0.20)	<0.001
Initial SPO_2 (%) ®		
100	1.00 (ref)	
90	0.57 (0.50 to 0.60)	<0.001
80	0.36 (0.28 to 0.48)	<0.001
70	0.26 (0.18 to 0.37)	<0.001
Initial blood sugar level (mmol/l)[µ]		
3	1.7 (1.5 to 1.9)	<0.001
7	1.00 (ref)	
10	0.75 (0.70 to 0.80)	<0.001
20	0.37 (0.29 to 0.47)	<0.001
Glasgow Coma Scale [χ]		
3	1.00 (ref)	
6	1.69 (1.60 to 1.70)	<0.001
9	4.02 (3.68 to 4.39)	<0.001
12	13.60 (11.52 to 16.06)	<0.001
15	65.15 (49.94 to 85.00)	<0.001
Respiratory rate (per minute)	0.99 (0.98 to 1.00)	0.20
Systolic blood pressure (mmHg)[¥]		
50	1.03 (1.02 to 1.06)	<0.001
90	1.00 (ref)	
120	0.94 (0.90 to 0.97)	<0.001
160	0.81 (0.73 to 0.91)	<0.001
Pulse rate(per minute)[◊]		
50	0.99 (0.99 to 1.00)	<0.001
100	1.00 (ref)	
120	1.001 (1.00 to 1.002)	<0.001
160	1.001 (1.00 to 1.002)	<0.001
Sex		<0.001
Female	1.00 (ref)	
Male	0.72 (0.62 to 0.85	
Rapid Sequence Intubation		0.25
No-RSI	1.00 (ref)	
RSI	0.86 (0.67 to 1.11)	

*Age fitted as fractional polynomial term $\beta 1$ $(age+1/100)^3$; ®Initial SPO_2 fitted as fractional polynomial term $\beta 1$ $(SPO_2+1/100)^3$; †Elixhauser fitted as fractional polynomial terms $\beta 1$ $(Elixhauser+1/10)^2$; χ Glasgow Coma Scale fitted as fractional polynomial terms $\beta 1$ $(GCS/10)^2$; ¥ Systolic BP fitted as fractional polynomial term $\beta 1$ (systolic $BP+1/100)^3$; ◊Pulse rate fitted as fractional polynomial term $\beta 1$ $(pulse+1/100)^{-1}$

Table S1B Estimates of a logistic regression model of RSI adjusted for covariates in 29,457 ischemic st

Factor	Adjusted OR (95% CI)	P-value
Age (years)*		
40	1.00 (ref)	
60	0.97 (0.96 to 0.97)	<0.001
80	0.92 (0.91 to 0.93)	<0.001
Elixhauser-Walraven score†		
10	1.00 (ref)	
20	0.84 (0.81 to 0.87)	<0.001
30	0.63 (0.57 to 0.69)	<0.001
40	0.42 (0.34 to 0.50)	<0.001
Initial SPO_2 (%) ®		
100	1.00 (ref)	
90	0.63 (0.56 to 0.71)	<0.001
80	0.43 (0.35 to 0.54)	<0.001
70	0.32 (0.24 to 0.43)	<0.001
Initial blood sugar level (mmol/l)	0.95 (0.94 to 0.96)	<0.001
Glasgow Coma Scale χ		
3	1.00 (ref)	
6	1.19 (1.18 to 1.20)	<0.001
9	1.92 (1.85 to 1.99)	<0.001
12	4.86 (4.46 to 5.29)	<0.001
15	22.43 (18.96 to 26.53)	<0.001
Respiratory rate (per minute)	0.96 (0.95 to 0.97)	<0.001
Pulse rate (per minute	0.99 (0.99 to 1.00)	0.053
Year	1.04 (1.02 to 1.07)	<0.001
Rapid Sequence Intubation		0.01
No-RSI	1.00 (ref)	
RSI	0.67 (0.49 to 0.91)	

*Age fitted as fractional polynomial term $\beta 1$ $(age+1/100)^3$; ® SPO_2 fitted as fractional polynomial term $\beta 1$ $(SPO_2+1/100)^3$; †Elixhauser fitted as fractional polynomial terms $\beta 1$ $(Elixhauser/10)^2$; χ Glasgow Coma Scale fitted as fractional polynomial terms $\beta 1$ $(GCS/10)^3$;

Table S1C Estimates of a logistic regression model of RSI adjusted for covariates in 14,374 haemorrhagic s

Factor	Adjusted OR (95% CI)	P-value
Response duration	1.001 (1.00 to 1.01)	0.001
Age (years)∗		
40	1.00 (ref)	
60	0.91 (0.90 to 0.92)	<0.001
80	0.80 (0.78 to 0.82)	<0.001
Elixhauser-Walraven score†		
10	1.00 (ref)	
20	1.95 (1.68 to 2.27)	<0.001
30	2.62 (2.22 to 3.36)	<0.001
40	3.13 (2.42 to 4.04)	<0.001
Initial SPO_2 (%) ®		
100	1.00 (ref)	
90	0.49 (0.42 to 0.59)	<0.001
80	0.28 (0.21 to 0.39)	<0.001
70	0.18 (0.12 to 0.28)	<0.001
Respiratory rate≈		
5	1.00 (ref)	
10	1.02 (1.00 to 1.04)	0.01
20	1.03 (1.01 to 1.05)	0.01
30	1.03 (1.01 to 1.05)	0.01
Initial blood sugar level (mmol/l)	0.96 (0.94 to 0.98)	<0.001
Glasgow Coma Scale χ		
3	1.00 (ref)	
6	1.47 (1.43 to 1.51)	<0.001
9	2.80 (2.60 to 3.02)	<0.001
12	6.92 (6.01 to 7.95)	<0.001
15	22.06 (17.63 to 27.61)	<0.001
Systolic blood pressure (mmHg)¥		
50	1.05 (1.04 to 1.06)	<0.001
90	1.00 (ref)	
120	0.92 (0.90 to 0.94)	<0.001
160	0.76 (0.71 to 0.82)	<0.001
Rapid Sequence Intubation		0.01
No-RSI	1.00 (ref)	
RSI	0.44 (0.33 to 0.58)	

∗Age fitted as fractional polynomial term $\beta 1$ $(age+1/100)^2$; ® SPO_2 fitted as fractional polynomial term $\beta 1$ $(SPO_2+1/100)^3$; †Elixhauser fitted as fractional polynomial terms β1 $(Elixhauser/10)^{-0.5}$; χ Glasgow Coma Scale fitted as fractional polynomial terms β1 $(GCS/10)^2$; ≈Respiratory rate fitted as fractional polynomial term $\beta 1$ $(respiratory\ rate+1/10)^{-2}$; ¥ Systolic BP fitted as fractional polynomial term $\beta 1$ $(systolic\ BP+1/100)^3$

Table C1.6 – 25: Rapid sequence intubation interaction of factors

A	Age < 58 years		Age ≥ 58 years		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for older vs younger age within strata*
Haemorrhagic stroke	61/102	**1.0 (REF)**	57/367	0.2 (0.1 – 0.4); p<0.001	0.2 (0.1 – 0.4); p<0.001
Ischemic stroke	34/33	1.1 (0.6 – 2.1);p=0.73	74/108	0.6 (0.4 – 1.0); p=0.06	0.5 (0.3 – 1.0); p=0.06
Traumatic brain injury	599/135	6.6 (4.3 – 10.1); p<0.001	139/157	1.3 (0.8 – 2.0); p=0.27	0.2 (0.1 – 0.3); p<0.001
No-RSI					
Haemorrhagic stroke	2,571/ 423	**1.0 (REF)**	5,869/ 3,075	0.2 (0.2 – 0.3); p<0.001	0.2 (0.2 – 0.3); p<0.001
Ischemic stroke	3,107/ 291	1.4 (1.2 – 1.8); p=0.001	20,750/ 3,662	0.6 (0.5 – 0.7); p<0.001	0.4 (0.3 – 0.5); p<0.001
Traumatic brain injury	33,293/252	10.6 (8.6 – 12.9); p<0.001	19,666/ 1,662	0.8 (0.7 – 0.9); p=0.004	0.1 (0.07 – 0.1); p<0.001

Estimates are adjusted for GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure and Elixhauser comorbidity score. Fifty eight was the mean age of the sample. Relative excess risk due to interaction for combined strokes vs. TBI for older vs younger age is -4.5 (-6.6 – -2.3); p<0.001 for RSI and -7.8 (-9.4 - -6.2); p<0.001for no-RSI.

B	Female		Male		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for male vs female within strata*
Haemorrhagic stroke	58/259	**1.0 (REF)**	60/211	1.4 (0.9 – 2.3); p = 0.18	1.5 (0.9 – 2.5);p=0.12
Ischemic stroke	44/67	3.2 (1.8- 5.7); p<0.001	64/74	2.6 (1.5 - 4.4); p=0.001	0.9 (0.5 – 1.6);p=0.73
Traumatic brain injury	195/73	8.7 (5.3 – 14.2); p<0.001	544/220	6.2 (4.1 – 9.4); p<0.001	0.7 (0.5 – 1.0);p=0.07
No-RSI					
Haemorrhagic stroke	4,305/ 1,840	**1.0 (REF)**	4,135/ 1,659	0.9 (0.8 – 1.0); p=0.004	0.8 (0.7 – 0.9); p<0.001
Ischemic stroke	11,031/ 2,155	3.0 (2.7 – 3.3); p<0.001	12,831/ 1,801	2.9 (2.6 – 3.1); p<0.001	1.1 (1.0 – 1.2); p=0.06
Traumatic brain injury	19,031/ 799	4.9 (4.4 – 5.5); p<0.001	33,954/ 1,115	4.3 (3.9 – 4.7); p<0.001	0.7 (0.7 – 0.8); p<0.001

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, Elixhauser comorbidity score

Relative excess risk due to interaction for combined strokes vs. TBI for female vs male is 0.07 (-0.04 – 0.18);p=0.23 for RSI and -0.04 (-0.1 - -0.01); p=0.005 for no-RSI

C	Shorter scene time (<24 minutes)		Longer scene time (≥24 minutes)		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for increased vs decreased scene time within strata*
Haemorrhagic stroke	9/29	**1.0 (REF)**	108/441	1.3 (0.5 – 3.3);p=0.63	1.3 (0.5 – 3.5);p=0.66
Ischemic stroke	9/10	4.0 (1.0 – 16.1);p=0.06	99/130	3.0 (1.1 – 8.1);p=0.03	0.8 (0.3 – 2.5);p=0.74
Traumatic brain injury	42/14	8.6 (2.7 – 27.5); p<0.001	684/277	7.1 (2.7 – 18.5); p<0.001	0.8 (0.4 – 1.6);p=0.54
No-RSI					
Haemorrhagic stroke	5,478 / 1,670	**1.0 (REF)**	2,919 /1,815	0.8 (0.8 – 0.9); p<0.001	0.8 (0.7 – 0.9); p<0.001
Ischemic stroke	17,225 / 2,094	3.5 (3.2 – 3.8); p<0.001	6,584 /1,849	2.2 (2.0 – 2.4); p<0.001	0.7 (0.6 – 0.7); p<0.001
Traumatic brain injury	32,754 /814	5.0 (4.5 – 5.6); p<0.001	20,030 /1,094	4.0 (3.7 – 4.5); p<0.001	0.8 (0.8 – 0.9); p=0.003

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure and Elixhauser comorbidity score. 24 minutes was the mean scene time

Relative excess risk due to interaction for combined strokes vs. TBI for unchanged/increased shorter versus longer scene times is -0.8 (-4.5 – 2.9); p=0.66 for RSI and -0.07(-0.3 - 0.2); p=0.53 for no-RSI.

D	Shorter time to RSI(<39 minutes)		Longer time to RSI(≥39 minutes)		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for shorter vs longer time-to-RSI within strata*
Haemorrhagic stroke	44/174	**1.0 (REF)**	59/235	0.7 (0.4 – 1.2);p=0.19	0.8 (0.4 – 1.4);p=0.37
Ischemic stroke	41/52	2.5 (1.3 – 4.7);p=0.01	55/69	1.9 (1.0 – 3.4);p=0.04	0.7 (0.4 – 1.5);p=0.37
Traumatic brain injury	308/152	3.9 (2.5 – 6.3); p<0.001	316/102	5.1 (3.1 – 8.3); p<0.001	1.3 (0.9 – 1.9);p=0.22

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure and Elixhauser comorbidity score. 39 minutes is the mean time to RSI.
Relative excess risk due to interaction for combined strokes vs. TBI for midazolam vs none = 1.09 (-0.1 – 2.3);p=0.08 for RSI

E	Intubation failure		Intubation success		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for success vs failure within strata*
Haemorrhagic stroke	3/14	**1.0 (REF)**	115/455	1.3 (0.2 – 7.6); p=0.76	1.5 (0.2 – 8.8);p=0.67
Ischemic stroke	3/2	11.4 (0.8 – 157.2); p=0.07	105/138	3.1 (0.5 – 18.3); p=0.21	0.3 (0.04 – 2.2);p=0.23
Traumatic brain injury	15/6	14.1 (1.8 – 113.2); p=0.01	719/287	7.3 (1.3 – 41.8); p=0.03	0.5 (0.1 – 1.6);p=0.22

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, Elixhauser comorbidity score
Relative excess risk due to interaction for combined strokes vs. TBI for intubation success vs failure = -2.3 (-9.6 – 5.0); p=0.54

F	Intubation attempts (one)		Intubation attempts (two or more)		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for one vs two or more intubation attempts within strata*
Haemorrhagic stroke	87/379	**1.0 (REF)**	18/40	2.9 (1.4 – 6.0); p=0.004	2.9 (1.4 – 6.3);p=0.01
Ischemic stroke	86/109	2.9 (1.8 – 4.2); p<0.001	10/9	4.8 (1.5 – 15.9); p=0.01	1.6 (0.5 – 4.8);p=0.43
Traumatic brain injury	594/239	6.6 (4.6 – 9.4); p<0.001	71/23	8.4 (4.5 – 15.8); p<0.001	1.2 (0.7 – 2.3);p=0.47

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, Elixhauser comorbidity score
Relative excess risk due to interaction for combined strokes vs. TBI for one attempt vs two or more = 0.92 (0.5 – 1.3); p<0.001

G	No- atropine		Atropine		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for atropine vs No-atropine within strata*
Haemorrhagic stroke	87/353	1.0 (REF)	31/117	0. 8 (0.5 - 1.4); p = 0.40	1.1 (0.6 – 1.9);p=0.86
Ischemic stroke	91/119	2.3 (1.5- 3.6); p<0.001	17/22	2.3 (1.1 - 5.1); p=0.04	0.9 (0.4 – 2.1);p=0.90
Traumatic brain injury	585/214	6.1 (4.3 - 8.7); p<0.001	154/79	3.5 (2.2 – 5.4); p<0.001	0.5 (0.4 – 0.7);p=0.001
No-RSI					
Haemorrhagic stroke	8,432/3,460	1.0 (REF)	8/39	0.2 (0.07 - 0.4); p<0.001	0.2 (0.07 – 0.4); p<0.001
Ischemic stroke	23,826/3,930	3.1 (2. – 3.3); p<0.001	36/26	1.6 (0.9 – 3.0); p=0.13	0.7 (0.4 – 1.3); p=0.25
Traumatic brain injury	52,957/1,881	4.9 (4.6 – 5.3); p<0.001	28/33	0.7 (0.4 – 1.3); p=0.29	0.1 (0.07 – 0.3); p<0.001

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, Elixhauser comorbidity score
Relative excess risk due to interaction for combined strokes vs. TBI for atropine vs. none is -0.06 (-0.2 – 0.05); p=0.31 for RSI and -1.4 (-1.7 – -1.1); p<0.001 for no-RSI.

H	No- fentanyl		Fentanyl		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for fentanyl vs. no-fentanyl within strata*
Haemorrhagic stroke	2/16	**1.0 (REF)**	116/454	4.2 (0.5 – 34.8); p = 0.18	5.9 (0.7 – 50.2);p=0.10
Ischemic stroke	10/7	11.7 (1.1- 130.1); p=0.045	98/134	9.7 (1.2 - 80.9); p=0.04	0.7 (0.2 – 2.3);p=0.54
Traumatic brain injury	175/75	15.9 (1.9 – 132.8); p=0.01	564/218	25.8 (3.1 – 212.3); p=0.003	1.7 (1.1 – 2.6);p=0.02
No-RSI					
Haemorrhagic stroke	8,148/3,399	**1.0 (REF)**	292/100	0.8 (0.6 – 1.1); p=0.12	0.8 (0.6 – 1.1); p=0.24
Ischemic stroke	23,519/3,870	3.1 (2.9 – 3.4); p<0.001	343/86	1.9 (1.5 – 2.6); p<0.001	0.7 (0.5 – 0.9); p=0.006
Traumatic brain injury	48,381/1,804	4.7 (4.4 – 5.1); p<0.001	4,604/110	6.2 (5.0 – 7.7); p<0.001	1.3 (0.99 – 1.6); p=0.05

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, Elixhauser comorbidity score

Relative excess risk due to interaction for combined strokes vs. TBI for fentanyl vs none is 0.17 (0.03 – 0.30); p=0.01 for RSI and -0.06 (-0.1 - 0.0002); p=0.05for no-RSI.

I	No- midazolam		Midazolam		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for midazolam vs no-midazolam within strata*
Haemorrhagic stroke	4/17	**1.0 (REF)**	114/453	1.8 (0.4 – 7.2); p = 0.42	2.2 (0.5 – 9.7);p=0.30
Ischemic stroke	8/4	4.6 (0.6- 33.1); p=0.13	100/137	4.2 (1.0 - 17.1); p=0.045	0.7 (0.2 – 2.9);p=0.61
Traumatic brain injury	256/74	9.9 (2.5 – 40.1); p=0.001	483/219	10.0 (2.5 – 40.0); p=0.001	0.9 (0.6 – 1.5);p=0.79
No-RSI					
Haemorrhagic stroke	8,321/3,354	**1.0 (REF)**	119/145	1.3 (0.9 – 1.7); p=0.15	1.1 (0.8 – 1.5); p=0.59
Ischemic stroke	23,747/3,882	3.1 (2.9 – 3.4); p<0.001	115/74	4.9 (3.3 – 7.1); p<0.001	2.0 (1.4 – 3.0); p<0.001
Traumatic brain injury	52,709/1,844	4.9 (4.6 – 5.3); p<0.001	276/70	4.5 (3.2 – 6.3); p<0.001	0.9 (0.7 – 1.4); p=0.76

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, Elixhauser comorbidity score

Relative excess risk due to interaction for combined strokes vs. TBI for midazolam vs none = -0.25 (-2.7 – 2.2);p=0.84 for RSI and -0.08 (-0.9 - 0.8); p=0.85 for no-RSI

J	No midazolam/morphine infusion		Midazolam/morphine infusion		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for infusion vs no-infusion within strata*
Haemorrhagic stroke	19/89	**1.0 (REF)**	99/381	1.3 (0.6 – 2.4); p = 0.51	1.4 (0.7 – 2.8);p=0.41
Ischemic stroke	18/33	2.0 (0.8- 4.9); p=0.15	90/108	3.2 (1.6 - 6.5); p=0.001	1.5 (0.7 – 3.3);p=0.34
Traumatic brain injury	98/54	6.2 (3.0 – 12.8); p<0.001	641/239	7.1 (3.7 – 13.6); p<0.001	1.1 (0.7 – 1.9);p=0.57
No-RSI					
Haemorrhagic stroke	8,347/ 3,351	**1.0 (REF)**	93/148	1.3 (1.0 – 1.8); p=0.09	1.1 (0.8 – 1.5); p=0.73
Ischemic stroke	23,815/ 3,881	3.2 (3.0 – 3.4); p<0.001	47/75	2.0 (1.3 – 3.2); p=0.002	1.1 (0.7 – 1.8); p=0.64
Traumatic brain injury	52,784/ 1,810	5.0 (4.6 – 5.4); p<0.001	201/104	3.3 (2.4 – 4.3); p<0.001	0.6 (0.4 – 0.8); p=0.001

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, Elixhauser comorbidity score

Relative excess risk due to interaction for combined strokes vs. TBI for infusion vs none = 0.3 (-1.9 – 2.6);p=0.77 for RSI and -0.4 (-0.9 - 0.2); p=0.20 for no-RSI

J	No midazolam/morphine infusion		Midazolam/morphine infusion		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); P for infusion vs no-infusion within strata*
Haemorrhagic stroke	19/89	**1.0 (REF)**	99/381	1.3 (0.6 – 2.4); p = 0.51	1.4 (0.7 – 2.8);p=0.41
Ischemic stroke	18/33	2.0 (0.8- 4.9); p=0.15	90/108	3.2 (1.6 - 6.5); p=0.001	1.5 (0.7 – 3.3);p=0.34
Traumatic brain injury	98/54	6.2 (3.0 – 12.8); p<0.001	641/239	7.1 (3.7 – 13.6); p<0.001	1.1 (0.7 – 1.9);p=0.57
No-RSI					
Haemorrhagic stroke	8,347/ 3,351	**1.0 (REF)**	93/148	1.3 (1.0 – 1.8); p=0.09	1.1 (0.8 – 1.5); p=0.73
Ischemic stroke	23,815/ 3,881	3.2 (3.0 – 3.4); p<0.001	47/75	2.0 (1.3 – 3.2); p=0.002	1.1 (0.7 – 1.8); p=0.64
Traumatic brain injury	52,784/ 1,810	5.0 (4.6 – 5.4); p<0.001	201/104	3.3 (2.4 – 4.3); p<0.001	0.6 (0.4 – 0.8); p=0.001

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, Elixhauser comorbidity score

Relative excess risk due to interaction for combined strokes vs. TBI for infusion vs none = 0.3 (-1.9 – 2.6);p=0.77 for RSI and -0.4 (-0.9 - 0.2); p=0.20 for no-RSI

K	Unchanged systolic blood pressure		Decreased systolic blood pressure		Increased systolic blood pressure		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); p for BP change within strata (unchanged BP as reference)*
Haemorrhagic stroke	6/23	**1.0 (REF)**	76/313	1.1 (0.3 – 3.7);p=0.91	35/129	0.7 (0.2 – 2.5);p=0.60	Decreased BP: 1.0 (0.3 – 3.7);p=0.96 Increased BP: 0.7 (0.2 – 2.5);p=0.55
Ischemic stroke	5/8	1.9 (0.3 – 11.0);p=0.47	57/90	2.0 (0.6 – 6.9);p=0.29	41/41	2.8 (0.8 – 10.1);p=0.13	Decreased BP: 0.9 (0.2 – 3.2);p=0.84 Increased BP: 1.3 (0.3 – 5.0);p=0.70
Traumatic brain injury	45/10	7.3 (1.8 – 29.5);p-0.01	344/164	5.4 (1.6 – 17.9);p=0.01	341/116	5.0 (1.5 – 17.0);p=0.01	Decreased BP: 0.7 (0.3 – 1.6);p=0.44 Increased BP: 0.7 (0.3 – 1.6);p=0.41
No-RSI							
Haemorrhagic stroke	2,488/873	**1.0 (REF)**	2,989/1, 212	1.0 (0.9 – 1.2);p=0.46	2,085/ 1,114	0.8 (0.7 – 0.9);p=0.001	Decreased BP: 1.1 (1.0 – 1.3);p=0.11 Increased BP: 0.8 (0.7 – 0.9); p<0.001
Ischemic stroke	7,628/1,22 7	2.9 (2.6 – 3.2);p<0.001	8,473/1, 288	3.2 (2.9 – 3.6); p<0.001	6,565/ 1,161	2.9 (2.6 – 3.3); p<0.001	Decreased BP: 1.0 (0.9 – 1.1);p=0.44 Increased BP: 1.1 (1.0 – 1.2);p=0.15
Traumatic brain injury	15,944/493	4.5 (4.0 – 5.2) p<0.001	19,156/5 70	5.5 (4.8 – 6.3); p<0.001	12,956 /659	3.9 (3.4 – 4.4); p<0.001	Decreased BP: 1.3 (1.1 – 1.5);p=0.002 Increased BP: 0.8 (0.7 – 1.0);p=0.01

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, and Elixhauser comorbidity score.

Relative excess risk due to interaction for combined strokes vs. TBI for unchanged/increased systolic BP vs decreased = -0.08 (-1.4 – 1.3); p=0.90 for RSI and -0.6(-0.9 - -0.3); p=0.001 for no-RSI.

L	Unchanged respiratory rate		Decreased respiratory rate		Increased respiratory rate		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); p for RR change within strata (unchanged RR as reference)*
Haemorrhagic stroke	19/78	**1.0 (REF)**	77/291	0.8 (0.4 – 1.7);p=0.63	20/94	0.8 (0.4 – 1.8);p=0.60	Decreased RR: 0.8 (0.4 – 1.6);p=0.56 Increased RR: 0.7 (0.3 – 1.6);p=0.41
Ischemic stroke	19/29	2.4 (1.0 – 5.8);p=0.06	72/84	2.2 (1.1 – 4.5);p=0.03	12/26	1.5 (0.6 – 4.0);p=0.43	Decreased RR: 1.2 (0.6 – 2.6);p=0.60 Increased RR: 0.5 (0.2 – 1.4);p=0.18
Traumatic brain injury	128/47	5.2 (2.5 – 10.7);p<0.001	486/177	5.4 (2.8 – 10.3);p<0.001	109/65	3.5 (1.7 – 7.0);p=0.001	Decreased RR: 1.0 (0.6 – 1.6);p=0.91 Increased RR: 0.7 (0.4 – 1.2);p=0.20
No-RSI							
Haemorrhagic stroke	5,803/2,117	**1.0 (REF)**	1,297/672	1.0 (0.9 – 1.1);p=0.96	382/410	0.6 (0.5 – 0.7); p<0.001	Decreased RR: 1.0 (0.9 – 1.2);p=0.74 Increased RR: 0.6 (0.5 – 0.7); p<0.001
Ischemic stroke	17,871/2,579	3.2 (2.9 – 3.4);p<0.001	3,566/759	3.1 (2.7 – 3.4); p<0.001	1,052/326	2.4 (2.0 – 2.7); p<0.001	Decreased RR: 1.1 (0.9 – 1.2);p=0.35 Increased RR: 0.8 (0.7 – 0.9);p=0.008
Traumatic brain injury	35,135/1,130	4.7 (3.3 – 5.2) p<0.001	11,831/386	5.4 (4.8 – 6.2); p<0.001	2,185/218	3.2 (2.7 – 3.9); p<0.001	Decreased RR: 1.0 (0.9 – 1.1);p=0.90 Increased RR: 0.6 (0.5 – 0.8); p<0.001

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, and Elixhauser comorbidity score. RR=respiratory rate

Relative excess risk due to interaction for combined strokes vs. TBI for unchanged/increased respiratory rate vs decreased is -0.99 (-2.5 – 0.5); p=0.19 for RSI and -0.5(-0.9 – -0.1); p=0.008 for no-RSI. 33

M	Unchanged $ETCO_2$		Decreased $ETCO_2$		Increased $ETCO_2$		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); p for $ETCO_2$ change within strata (unchanged ETCO2 as reference)*
Haemorrhagic stroke	15/42	**1.0 (REF)**	57/238	0.6 (0.3 – 1.3);p=0.21	45/171	0.5 (0.2 – 1.2);p=0.11	Decreased BP: 0.7 (0.3 – 1.4);p=0.31 Increased BP: 0.6 (0.2 – 1.3);p=0.16
Ischemic stroke	12/14	2.0 (0.6 – 6.7);p=0.25	48/66	1.2 (0.5 – 2.8);p=0.66	42/57	1.4 (0.6 – 3.3);p=0.40	Decreased BP: 0.7 (0.3 – 2.0);p=0.51 Increased BP: 0.8 (0.3 – 2.2);p=0.62
Traumatic brain injury	59/18	5.7 (2.2 – 14.4);p-0.01	424/159	3.3 (1.6 – 6.9);p=0.001	218/106	3.0 (1.4 – 6.4);p=0.004	Decreased BP: 0.6 (0.3 – 1.1);p=0.11 Increased BP: 0.5 (0.3 – 1.1);p=0.08

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, and Elixhauser comorbidity score.
Relative excess risk due to interaction for combined strokes vs. TBI for unchanged/increased $ETCO_2$ vs decreased = -0.6 (-2.2 – 0.9);p=0.43 for RSI

N	Unchanged SPO_2		Decreased SPO_2		Increased SPO_2		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); p for change of SPO2 within strata (unchanged SPO2 as reference)*
Haemorrhagic stroke	32/113	**1.0 (REF)**	15/46	1.2 (0.5 – 2.9);p=0.64	69/307	0.9 (0.5 – 1.6);p=0.81	Decreased: 0.9 (0.4 – 2.4);p=0.90 Increased: 0.9 (0.5 – 1.6);p=0.62
Ischemic stroke	15/29	1.8 (0.8 – 4.2);p=0.19	9/9	3.1 (0.9 – 10.4);p=0.07	78/98	2.5 (1.4 – 4.5);p=0.003	Decreased: 1.9 (0.5 – 6.9);p=0.31 Increased: 1.3 (0.6 – 2.9);p=0.47
Traumatic brain injury	219/63	8.0 (4.5 – 14.3);p=0.001	39/34	2.7 (1.4 – 5.5);p=0.005	469/191	5.5 (3.3 – 9.3); p<0.001	Decreased: 0.3 (0.2 – 0.6);p=0.001 Increased: 0.7 (0.5 – 1.0);p=0.06
No-RSI							
Haemorrhagic stroke	2,288/ 818	**1.0 (REF)**	650/27 1	0.8 (0.7 – 1.0);p=0.03	1,248/ 1,083	0.7 (0.6 – 0.8); p<0.001	Decreased: 0.8 (0.7 – 1.0);p=0.05 Increased: 0.6 (0.6 – 0.7); p<0.001
Ischemic stroke	7,231/91 7	3.1 (2.7 – 3.5);p<0.001	2,060/2 72	3.0 (2.5 – 3.5); p<0.001	3,817/ 1,057	2.0 (1.8 – 2.3); p<0.001	Decreased : 1.0 (0.8 – 1.2);p=0.90 Increased : 0.7 (0.6 – 0.8); p<0.001
Traumatic brain injury	15,581/ 471	5.0 (4.3 – 5.7) p<0.001	4,491/ 124	5.2 (4.2 – 6.5); p<0.001	7,850/535	3.3 (2.9 – 3.8); p<0.001	Decreased : 1.1 (0.8 – 1.3);p=0.58 Increased : 0.7 (0.6 – 0.8); <0.001

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, and Elixhauser comorbidity score. RR=respiratory rate

Relative excess risk due to interaction for combined strokes vs. TBI for unchanged/increased SPO_2 vs decreased is 2.3 (0.9 – 3.7); p=0.001 for RSI and -0.4(-1.1 - 0.1); p=0.15 for no-RSI.

O	Unchanged pulse rate		Decreased pulse rate		Increased pulse rate		
RSI	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*No. with/without survive to discharge*	*OR (95% CI); P*	*OR (95% CI); p for pulse rate within strata (unchanged pulse rate as reference)*
Haemorrhagic stroke	4/24	1.0 (REF)	38/132	1.4 (0.4 – 5.3);p=0.60	75/309	1.0 (0.3 – 3.5);p=0.99	Decreased: 1.2 (0.3 – 4.7);p=0.75 Increased: 1.2 (0.3 – 4.4);p=0.81
Ischemic stroke	11/11	3.4 (0.7 – 16.0);p=0.12	47/55	3.4 (0.9 – 12.8);p=0.07	45/73	2.0 (0.5 – 7.6);p=0.29	Decreased: 1.0 (0.3 – 2.7);p=0.95 Increased: 0.5 (0.2 – 1.3);p=0.15
Traumatic brain injury	36/6	15.9 (3.3 – 76.5);p=0.001	309/90	9.6 (2.7 – 34.1);p<0.001	384/194	4.7 (1.3 – 16.6);p=0.02	Decreased: 0.6 (0.2 – 1.7);p=0.36 Increased: 0.3 (0.1 – 0.8);p=0.02
No-RSI							
Haemorrhagic stroke	2,398/ 807	1.0 (REF)	3,336/1, 407	0.9 (0.8 – 1.0);p=0.03	1,865/1, 013	0.8 (0.7 – 0.9); p=0.001	Decreased: 0.9 (0.8 – 1.0);p=0.03 Increased: 0.8 (0.7 – 0.9); p<0.001
Ischemic stroke	6,976/1,0 45	2.8 (2.5 – 3.2);p<0.001	10,004/1 ,478	3.0 (2.7 – 3.4); p<0.001	5,772/1, 178	2.5 (2.3 – 2.9); p<0.001	Decreased : 1.1 (1.0 – 1.2);p=0.19 Increased : 0.9 (0.8 – 1.0);p=0.04
Traumatic brain injury	12,958/ 457	4.1 (3.5 – 4.7) p<0.001	26,958/ 737	5.1 (4.5 – 5.8); p<0.001	9,793/55 4	3.5 (3.1 – 4.0); p<0.001	Decreased : 1.2 (1.0 – 1.3);p=0.04 Increased : 0.8 (0.7 – 1.0); p=0.03

Estimates are adjusted for age, GCS, sex, year, respiratory rate, pulse rate, systolic blood pressure, and Elixhauser comorbidity score. RR=respiratory rate

Relative excess risk due to interaction for combined strokes vs. TBI for unchanged/increased pulse rate vs decreased is -1.8 (-3.4 – 0.2); p=0.03 for RSI and -0.7(-1.0 – -0.5); p<0.001 for no-RSI.

Table S3 model Fit and performance statistics

Model	No. observations model fitted to	Hosmer and Lemeshow statistic (chi^2(DF); P)	Pseudo R^2	Area under curve	Bayesian Information Criterion
Baseline model for interactions	107,128	73.7(8); p<0.001	0.26	0.85	22823.1
Baseline model for interactions, random sample*	4,000	11.8(8);p=0.16	0.24	0.87	2146.3
Traumatic brain injury	63,297	39.7(8);p<0.001	0.35	0.91	5118.9
Traumatic brain injury, random sample*	4,000	5.8(8);p=0.67	0.33	0.89	456.9
Haemorrhagic Stroke	14,374	4.1(8);p=0.85	0.28	0.83	5635.5
Haemorrhagic Stroke, random sample*	4,000	10.8(8);p=0.21	0.28	0.83	1638.3
Ischemic stroke	29,457	33.6(8);p<0.001	0.22	0.83	10114.4
Ischemic stroke, random sample	4,000	12.1(8);p=0.15	0.24	0.83	1470.8

*Random sample of 4,000 observations

Chapter 2 figures

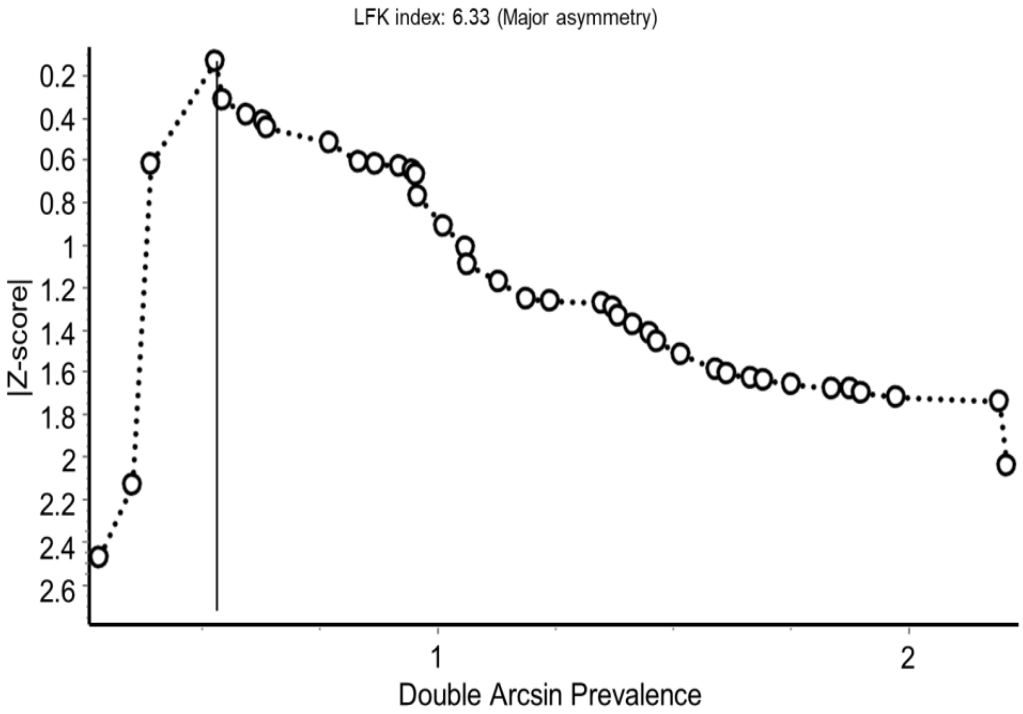


Figure C2.1. Doi plot of non-traumatic brain pathologies intubation prevalence, QE model

C.3 Chapter 4 figures

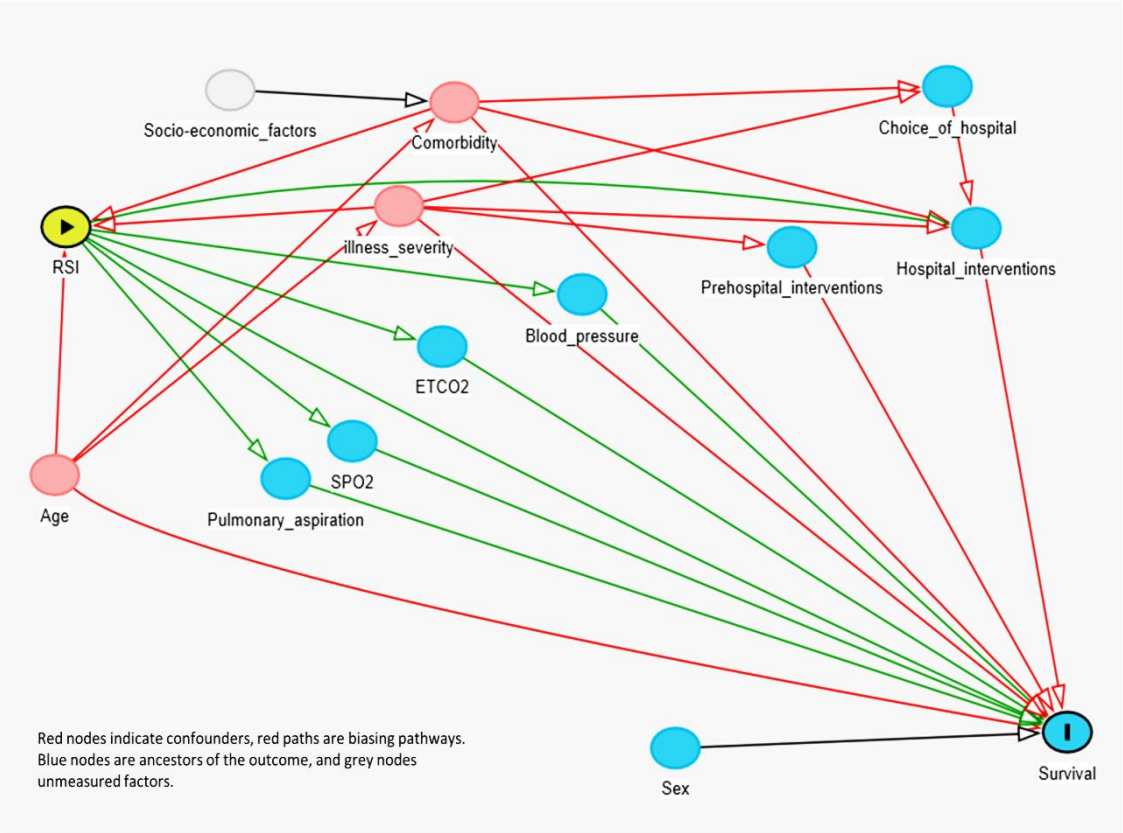


Figure C3.1. Directed acyclic graph of the causal path of RSI for survival.

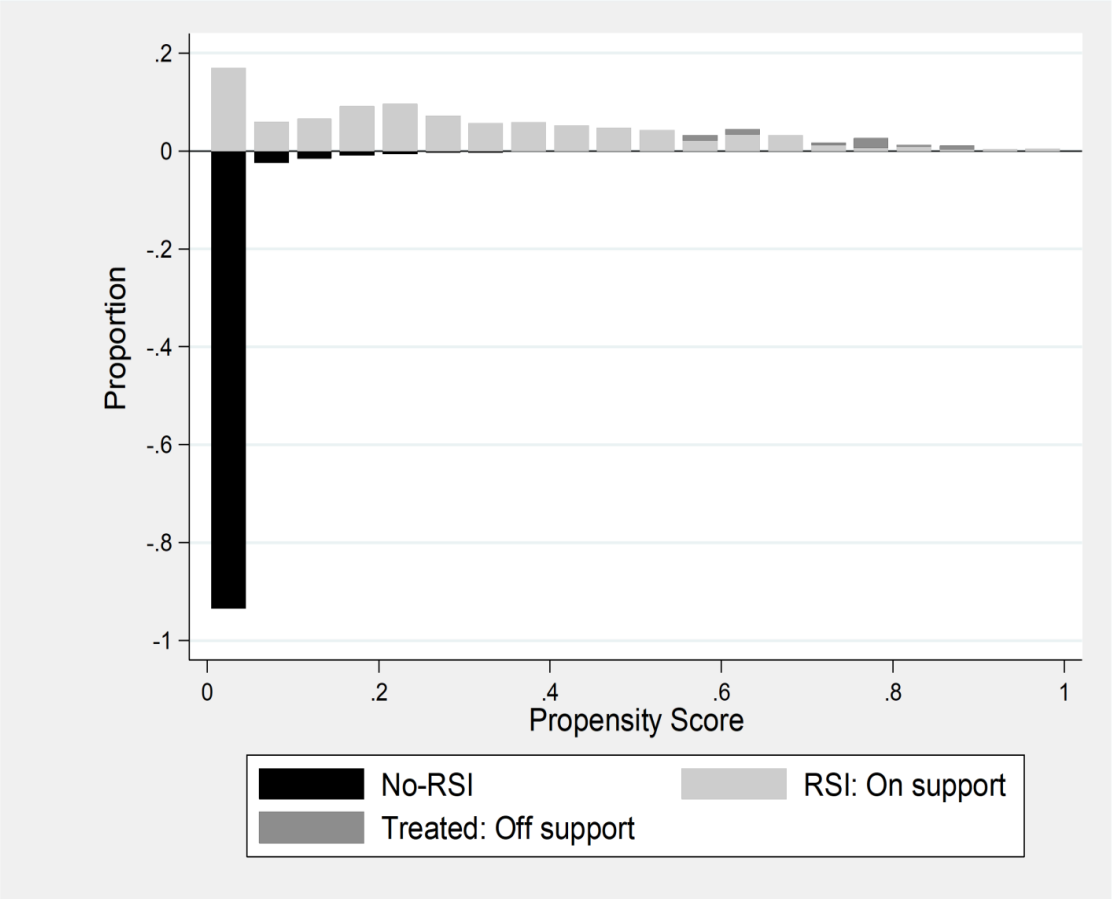


Figure C3.2. Distribution of propensity score across treatment and comparison groups in the unmatched cohort.

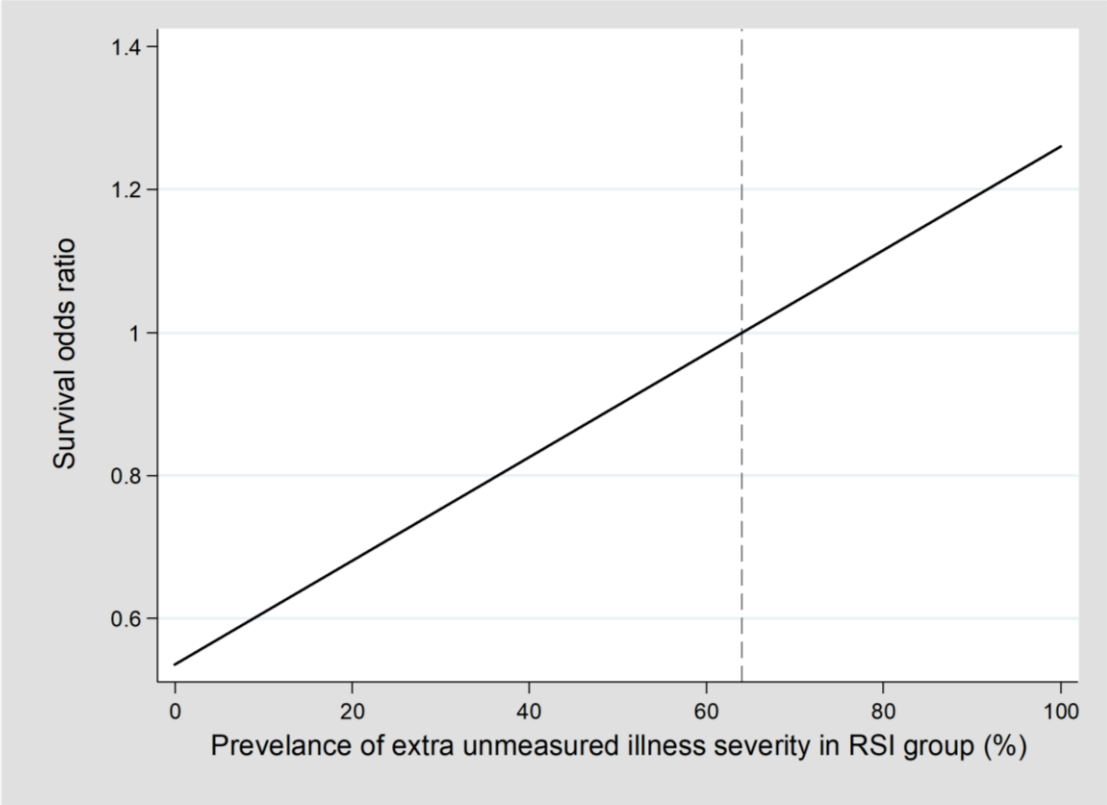


Figure C3.3. Effect of adjustment for additional unmeasured illness severity in the RSI cohort (dashed line at 64% prevalence in RSI group).

C.4 Chapter 4 letter to editor and response

Letter

Published on: 23 July 2019

Rapid sequence intubation (RSI) is uncommon in prehospital stroke care

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Other Contributors:

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Caroline L Watkins, Professor of Stroke and Older People's Care

As researchers with an interest in pre-hospital stroke care, we read this paper with interest, but also with some surprise at the authors' assertion that 'RSI is commonly used by paramedics in stroke'. On examining the cited studies and the authors' own findings more closely, this statement is hard to justify. Although Meyer et al did indeed report that 55% of out-of-hospital haemorrhagic strokes received RSI, this actually refers to a retrospective chart review of 20 children, all of whom with a Glasgow Coma Scale ≤ 8 following acute haemorrhagic stroke from a cerebral arteriovenous malformation rupture. This small, selective paediatric sample cannot be held to be representative of all stroke patients who are conveyed to hospital by emergency medical services. The other study cited as evidence found that people with acute stroke form a substantial proportion (36.6%) of RSIs undertaken by paramedics (Fouche et al., 2017). Whilst stroke may be a common reason for paramedic RSI, it cannot therefore be inferred that paramedic RSI is common in stroke. The authors' own findings bear this out: of their sample of nearly 44,000 stroke patients conveyed by the emergency medical services, only 2% had received paramedic RSI.

Whilst we congratulate the authors on their comprehensive analysis of this large dataset, it is important that readers do not gain the impression that paramedic RSI is frequently indicated and performed in pre-hospital stroke care.

Response

Published on: 2 September 2019

Prehospital rapid sequence intubation is not uncommon in unconscious stroke

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We thank Drs Gibson, Jones and Watkins for their interest in our paper and for pointing out that our statement that RSI is commonly used by paramedics may be incorrectly interpreted by readers. We agree that whilst RSI for traumatic and non-traumatic causes of coma are common in paramedic practice, it cannot be inferred that paramedic RSI is common in stroke. It would have been more accurate to say that paramedic RSI is not uncommon in stroke patients that are unconscious. In our dataset of 38,352 strokes 3,374 had an initial Glasgow Coma Scale of less than nine, of which 627 (18.6%) received RSI by our paramedics, but this was not reported in our paper. In our opinion, 18.6 % paramedic RSI in unconscious patients would qualify as common use of RSI.

Alternatively, we could have stated that the emergency use of intubation techniques such as RSI in the stroke patient is common. In our recent systematic review and meta-analysis it was demonstrated that emergency department and prehospital intubation via methods such as RSI is commonplace in strokes.1 This review shows that emergency endotracheal intubation was used in 79% of haemorrhagic, and 6% of ischemic strokes. In a sensitivity analysis, the removal of a large influential study raised the prevalence of

intubation in ischaemic strokes to 25%. We argue that most of these intubations were RSI, and we can therefore conclude that RSI in the emergency setting for strokes is frequent.

Ultimately we agree with Drs Gibson, Jones and Watkins in that our statement that RSI is commonly used by paramedics for stroke is not clear without qualification, but we hope they agree that RSI is indeed commonly used in unconscious stroke patients and in the emergency setting more broadly. If it is true that RSI is frequently used, and that there is a lack of high-quality evidence to support emergency intubation in stroke patients, then it is clear that a trial is needed.

Reference

1. Fouche PF, Stein C, Jennings PA, Boyle M, Bernard S, Smith K. Review article: Emergency endotracheal intubation in non-traumatic brain pathologies: A systematic review and meta-analysis. Emerg Med Australas 2019; 31(4): 533-41.

Conflict of Interest:

None declared.