Prehospital Rapid Sequence Intubation Improves Functional Outcome for Patients With Severe Traumatic Brain Injury

A Randomized Controlled Trial

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Objective: To determine whether paramedic rapid sequence intubation in patients with severe traumatic brain injury (TBI) improves neurologic outcomes at 6 months compared with intubation in the hospital.

Background: Severe TBI is associated with a high rate of mortality and long-term morbidity. Comatose patients with TBI routinely undergo endo-tracheal intubation to protect the airway, prevent hypoxia, and control ventilation. In many places, paramedics perform intubation prior to hospital arrival. However, it is unknown whether this approach improves outcomes.

Methods: In a prospective, randomized, controlled trial, we assigned adults with severe TBI in an urban setting to either prehospital rapid sequence intubation by paramedics or transport to a hospital emergency department for intubation by physicians. The primary outcome measure was the median extended Glasgow Outcome Scale (GOSe) score at 6 months. Secondary end-points were favorable versus unfavorable outcome at 6 months, length of intensive care and hospital stay, and survival to hospital discharge.

Results: A total of 312 patients with severe TBI were randomly assigned to paramedic rapid sequence intubation or hospital intubation. The success rate for paramedic intubation was 97%. At 6 months, the median GOSe score was 5 (interquartile range, 1–6) in patients intubated by paramedics compared with 3 (interquartile range, 1–6) in the patients intubated at hospital ($P = 0.28$). The proportion of patients with favorable outcome (GOSe, 5–8) was 80 of 157 patients (51%) in the paramedic intubation group compared with 56 of 142 patients (39%) in the hospital intubation group (risk ratio, 1.28; 95% confidence interval, 1.00–1.64; $P = 0.046$). There were no differences in intensive care or hospital length of stay, or in survival to hospital discharge.

Conclusions: In adults with severe TBI, prehospital rapid sequence intubation by paramedics increases the rate of favorable neurologic outcome at 6 months compared with intubation in the hospital.

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Severe traumatic brain injury (TBI) is a leading cause of death and long-term disability in developed countries, particularly in young adults.[1] After the initial injury, many patients suffer secondary brain injury because of hypoxia, hypercapnea, or hypotension, and this may have an adverse effect on outcome.[2] Current emergency medical management has the goal of preventing or promptly treating these secondary insults.

Early endotracheal intubation is commenced in hospitalized patients who are unconscious following severe TBI to insults ensure airway protection, adequate oxygenation and ventilation, and facilitate radiologic imaging.[3] In the emergency department (ED), rapid sequence intubation (RSI) involving administration of sedative drugs and a neuromuscular blocking drug is regarded as the optimal technique for endotracheal intubation.[4] However, the optimal airway management technique in the prehospital setting is uncertain. Many emergency medical services (EMS) in developed countries authorize endotracheal intubation without sedating and/or neuromuscular blocking drugs to facilitate endotracheal intubation.[5] Current data from observational studies suggest that this approach may be associated with a low success rate and worse outcomes compared with basic airway management in the field.[5,6]

An alternate approach is RSI performed by paramedics at the scene of the injury. This is used in some cities by paramedics in North America[7] and Australia[5,8] and by physician-staffed ambulances in some cities in Europe.[9] Whereas this approach has been reported as having a high procedural success rate, studies comparing paramedic RSI with hospital intubation in patients with severe TBI have been retrospective or uncontrolled, with conflicting results.[6,10]

We therefore conducted a prospective, randomized, controlled trial comparing paramedic RSI with hospital intubation in adults with severe TBI to determine whether this approach improves neurologic outcome at 6 months postinjury.

METHODS

Study Setting

The study was undertaken in 4 cities (Melbourne, Geelong, Ballarat, and Bendigo) in Victoria, Australia with enrollment between April 2004 and January 2008 and 6-month patient follow-up completed in July 2008. These cities have a combined population of approximately 4.0 million. In Victoria, there is a trauma system that designates that patients with major trauma be transported by the EMS to 1 of the 2 trauma hospitals in central Melbourne, with bypass of other hospitals if patient condition permits. There is a register of all patients with major trauma (The Victorian State Trauma Register) that has selected prehospital and hospital data for all patients with major trauma, including all patients with severe TBI. The register provided data for patients with severe TBI who were not enrolled in the study. This system has been described previously.[11]

The EMS in Victoria is 2-tier with approximately 1700 paramedics authorized to practice some advanced life support skills

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in trauma patients, including insertion of a laryngeal mask airway and administration of intravenous morphine for pain and crystalloid fluid for hypotension. In addition, there are 360 intensive care paramedics who are authorized to undertake endotracheal intubation, decompress suspected tension pneumothorax and administer a wider range of intravenous drugs. Intensive care paramedics are dispatched to patients with suspected major trauma, including patients reported by bystanders as being unconscious. Patients within 30 minutes of a trauma hospital are generally transported by road ambulance, whereas an intensive care paramedic-staffed helicopter is dispatched to patients with major trauma if road transport time to a designated trauma hospital is greater than 30 minutes. Patient management by paramedics follows medically determined, written clinical practice guidelines without on-line medical control (available at: www.ambulance.vic.gov.au/Paramedics/Qualified-Paramedic-Training/Clinical-Practice-Guidelines.html, accessed January 2010). Patients aged 15 years or older are treated using adult clinical practice guidelines and are transported to adult trauma hospitals.

For this study, intensive care paramedics on road ambulances in the 4 study cities undertook an additional 16-hour training program in the theory and practice of RSI, including class time (4 hours), practical intubating experience in the operating room under the supervision of an anesthesiologist (8 hours), and completion of a simulation-based examination (4 hours). Between January 2003 and March 2004, there was a study lead-in phase that authorized paramedics to undertake RSI in patients with severe TBI without randomization.

The National Health and Medical Research Council of Australia and the Victorian Transport Accident Commission provided funding for the trial.

Study Design

This study was a prospective, randomized, controlled trial. The study protocol was approved by ethics committee of Monash University, Victoria, Australia, and the institutional ethics committees at each receiving hospital. The requirement for informed patient consent was waived in accordance with Australian Government regulations. Next-of-kin and surviving patients were informed of the trial as soon as possible after enrollment and the 6-month follow-ups with the patient or next-of-kin were conducted with informed consent.

Study Patients

Patients were eligible for enrollment if they were assessed by paramedics on road ambulances as having all the following: evidence of head trauma, Glasgow Coma Score $\leq$9, age $\geq$15 years, and intact airway reflexes. Patients were excluded if any of the following applied: within 10 minutes of a designated trauma hospital, no intravenous access, allergy to any of the RSI drugs (as stated by relatives or a medical alert bracelet), or transport planned by medical helicopter.

Study Procedures

Eligible patients were randomized by the attending paramedic opening an opaque, sealed envelope that indicated treatment allocation. The allocation was computer randomized and allocated in blocks of 10 to each paramedic ambulance unit.

Patients allocated to paramedic intubation received preoxygenation using bag/mask for a minimum of 3 minutes. Monitoring included continuous pulse oximetry, end-tidal waveform capnography and electrocardiography. Drug therapy for intubation consisted of fentanyl (100μg), midazolam (0.1 mg/kg), and succinylcholine (1.5 mg/kg) administered in rapid succession. Atropine (1.2 mg) was administered for a heart rate $<$60/min. A minimum 500 mL fluid bolus (lactated Ringers Solution) was administered. A half dose of the sedative drugs was used in patients with hypotension (systolic blood pressure $<$100 mm Hg) or older age ($>$60 years). Cricoid pressure was applied in all patients. After intubation and confirmation of the position of the endotracheal tube using the presence of the characteristic wave-form on a capnograph, patients received a single dose of pancuronium (0.1 mg/kg), and an intravenous infusion of morphine and midazolam at 5 to 10 mg/h each. If intubation was not achieved at the first attempt, or the larynx was not visible, one further attempt at placement of the endotracheal tube over a plastic airway bougie was permitted. If this was unsuccessful, ventilation with oxygen using a bag/mask and an oral airway was commenced and continued until spontaneous respirations returned. Insertion of a laryngeal mask airway was indicated if bag/mask ventilation using an oral airway appeared to provide inadequate ventilation. Cricothyroidotomy was indicated if adequate ventilation could not be achieved with the above interventions.

Patients allocated to hospital intubation received high-flow (12 L/min) supplemental oxygen by mask and assisted bag/mask ventilation, if required. An oropharyngeal or nasopharyngeal airway was inserted if airway suctioning was required. A small dose of morphine (up to 5 mg intravenously) was permitted if the patient was combative. If the conscious state of the patient deteriorated during transport and airway reflexes were completely lost, endotracheal intubation (without sedative or neuromuscular blocking drugs) was permitted.

In all patients, a cervical collar was fitted, and hypotension (systolic blood pressure $<$100 mm Hg) was treated with a 20 mL/kg bolus of lactated Ringers Solution that could be repeated as indicated. Other injuries such as fractures were treated as required.

In the hospital emergency department, patients who were not intubated underwent immediate RSI by a physician prior to chest x-ray and computed tomography head scan. In these patients, arterial blood gases were performed only after intubation and insertion of an arterial cannula. Under Victorian state law, blood was collected from motor vehicle drivers for ethanol concentration analysis, but this result was not available in the medical record.

After initial evaluation and management in the emergency department, neurosurgical and intensive care management was at the discretion of the treating physicians, but generally followed the recommendations of the Brain Trauma Foundation (available at: http://www.braintrauma.org). For patients admitted to an Intensive Care Unit, most aspects of intensive care such as mechanical ventilation mode, fluid therapy, intracranial pressure control, cerebral perfusion pressure goals, blood transfusion, blood glucose control, and nutrition followed written guidelines in all patients. Corticosteroids were only administered in patients with low serum cortisol and high vasopressor requirements.

Study End Points

At 6 months following injury, surviving patients or their next-of-kin were interviewed by telephone using a structured questionnaire and allocated a score from 1 (deceased) to 8 (normal) using the extended Glasgow Outcome Scale (GOSe).[12] The interviewer was blinded to the treatment allocation.

For patients who were unable to be contacted by telephone, attempts were made to contact relatives who may have contact with the patient. In addition, a letter was sent to the last known address of the patient, requesting contact with the Research Coordinator of the study. Attempts to contact missing patients or their relatives were undertaken at regular intervals for up to 12 months postinjury.

Patients who were unable to be contacted after this time were considered lost to follow-up.

Statistical Analysis

On the basis of a previous study by our group,[13] the sample size was calculated to detect a change of 1 point in the median GOSe. The sample size estimate was increased by 20% to account for

non-normality of the data and loss to follow-up. This resulted in a sample size of 312 patients to achieve 80% power at an alpha error of 0.05.

There was a planned interim analysis of the 6-month outcomes after 150 patients had been enrolled. A $P < 0.001$ was designated as the threshold for stopping the study if there was evidence of significant benefit or harm in either arm of the study groups.

The secondary outcome measures were: the 6-month GOSe divided into 2 groups: unfavorable (GOSe scores, 1–4) and favorable (GOSe scores, 5–8), the duration of intensive care unit and hospital stay, and survival to hospital discharge. Three a priori subgroup analyses were planned: patients with an initial Glasgow Coma Score $\geq$5, patients aged $\leq$60 years, and patients with an EMS transport time greater than 20 minutes to the trauma hospital.

All patients allocated to each group were considered as comprising the intention-to-treat population for the primary and secondary analyses. Analysis of the principal outcome of GOSe at 6 months was performed using Mann-Whitney *U* test. Additional results are expressed as risk ratios with 95% confidence intervals, and compared using χ^2. Numerical variables that approximate a normal distribution are summarized as mean $\pm$ SD, and groups compared using t-tests. Non-normal variables are summarized as median ($\pm$ interquartile range), and groups compared using *U* tests. All reported *P* values are 2-sided.

Data Safety Monitoring

A data safety monitoring board was established. Serious adverse events reported to the data safety monitoring board were prehospital cardiac arrest and unrecognised esophageal intubation. An interim analysis of the 6-month outcomes after 150 patients had been enrolled was undertaken. Following this analysis, approval for continuation of the study was received.

RESULTS

Patients and Interventions

Between April 2004 and January 2008, a total of 1045 patients with suspected severe traumatic brain injury were evaluated by paramedics in the trial areas for possible enrollment in the trial (Fig. 1). Three hundred twenty-eight patients met the enrollment criteria. Three hundred twelve patients were randomly allocated to either paramedic intubation (160 patients) or hospital intubation (152 patients). There were 16 patients who were eligible but not enrolled because of paramedic error.

The baseline characteristics of all the patients enrolled in the study are shown in Table 1. The 2 groups were similar in all the major characteristics associated with outcome after severe TBI, including age, mechanism of injury, initial Glasgow Coma Score (GCS), degree of intracranial injury shown in the first CT head scan (Marshall score) and the Abbreviated Injury Score (head). The mean Injury Severity Score >25 indicates that many patients had multiple injuries.

Of 312 patients, 6 were determined to have a diagnosis other than TBI after evaluation in the emergency department, 3 in the paramedic intubation group, and 3 in the hospital intubation group. Of these, 5 had spontaneous intracranial hemorrhage followed by a fall and minor head strike. In one patient, the cause of the coma was drug overdose taken some hours following a minor head injury. The baseline characteristics and outcomes of these patients are included in the analyses, except for the Marshall CT brain scores.

The patient treatments and progress are shown in Table 2. Of the 160 patients allocated to paramedic intubation, 157 patients were administered RSI drugs and intubation attempted. There were 3 patients allocated to paramedic intubation but not administered the RSI drugs. In 2 patients, there was improvement in the Glasgow

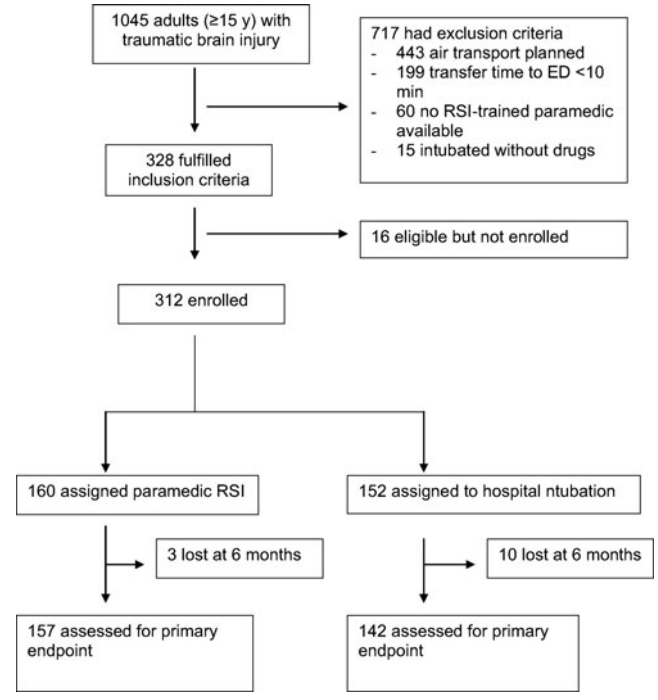

FIGURE 1. Trial profile. ED indicates emergency department, RSI, rapid sequence intubation.

Coma Score between enrollment and receiving any drugs and these patients were transported to hospital without intubation. In 1 patient, cardiac arrest occurred after randomization but prior to any drug administration. This patient was intubated during cardiopulmonary resuscitation without study drugs and transported to hospital. Of the 157 patients administered RSI drugs, intubation was successful in 152 (97%) patients. The remaining 5 patients had esophageal placement of the endotracheal tube recognized immediately on capnography. The endotracheal tube was removed and the patients were managed with an oropharyngeal airway and bag/mask ventilation with oxygen and transported to hospital.

Of the 152 patients allocated to hospital intubation, 144 (95%) arrived at the emergency department without intubation. In 5 patients, there was a decrease in conscious state and loss of airway reflexes during transport to hospital, and intubation was undertaken without supplemental drug therapy. In 2 patients, cardiac arrest occurred during transport and intubation was undertaken during cardiopulmonary resuscitation without supplemental drug therapy. In 1 patient, a medical helicopter became available after randomization and the patient was successfully intubated for the flight using RSI.

There were 10 cardiac arrests prior to hospital arrival in the paramedic RSI group and 2 in the patients allocated to hospital intubation. In the paramedic intubation group, asystolic cardiac arrest occurred in 1 patient immediately after randomization but prior to administration of any drugs (as above). The systolic blood pressure in this patient at randomization was 70 mm Hg. In another patient with an initial systolic blood pressure of 70 mm Hg, asystolic cardiac arrest occurred during administration of the intubating drugs. In 5 other patients, intubation was achieved and correct placement of the endotracheal tube was demonstrated by waveform capnography; however, these patients experienced cardiac arrest during transport. In 2 of these patients, the blood pressure was >100 mm Hg prior to intubation and in the remaining 3 of these 5 patients, the blood pressure was

TABLE 1. Baseline Characteristics of the Patients

Characteristic	Paramedic RSI Group (n = 160)	Hospital Intubation Group (n = 152)
Age, yr	40.0 ± 22	41.4 ± 23
Male sex, no. (%)	120 (75)	117 (77)
Mechanism of injury, no. (%)		
Vehicle occupant	42 (26)	38 (25)
Motorcyclist	12 (7.5)	7 (4.6)
Cyclist	6 (3.8)	10 (6.6)
Pedestrian	34 (21)	42 (28)
Fall	50 (31)	39 (26)
Assault	12 (7.5)	11 (7.2)
Penetrating	0	2 (1.3)
Other	4 (2.5)	3 (2.0)
Paramedic response time, min	17 ± 11	16 ± 10
Initial vital signs*		
Systolic BP, mm Hg	134 ± 36	129 ± 38
Heart rate, beats/min	96 ± 29	96 ± 27
Oxygen saturation, %	96 ± 3.9	96 ± 4.8
Initial GCS		
3	52	52
4	20	19
5	11	6
6	22	22
7	32	23
8	12	16
9	6	11
>9	4	3
Not recorded	1	0
GCS median (IQR)	5 (3−7)	5 (3−7)
CT findings (Marshall), no. (%)		
Normal	35 (24)	43 (30)
Diffuse injury, grade 2	62 (43)	55 (38)
Diffuse injury, grade 3	12 (8.3)	19 (13)
Diffuse injury, grade 4	7 (4.9)	9 (6.3)
Diffuse injury, grade 5	0	0
Diffuse injury, grade 6	28 (19)	18 (13)
Injury severity score*	30.5 ± 14.8	30.1 ± 14.5
No. injury severity score >15 (%)	37 (23)	28 (18)
Abbreviated injury severity scores		
AIS head = 0, no (%)	5 (3)	6 (4)
AIS head = 1, no (%)	6 (4)	5 (4)
AIS head = 2, no (%)	9 (6)	11 (8)
AIS head = 3, no (%)	15 (10)	23 (16)
AIS head = 4, no (%)	42 (30)	28 (20)
AIS head = 5, no (%)	68 (47)	68 (48)
AIS head*	4.0 ±1.4	3.9 ± 1.4
Face*	0.8 ± 1.0	1.0 ± 1.0
Chest*	0.2 ± 0.6	0.2 ± 0.6
Abdomen/pelvis*	1.8 ± 1.9	1.7 ± 1.9
Extremities*	0.5 ± 1.1	0.7 ± 1.3
Skin*	1.5 ± 1.3	1.6 ± 1.3

*Plus-minus values are means ± SD.

RSI indicates rapid sequence intubation; GCS, Glasgow Coma Scale; IQR, interquartile range; CO_2, carbon dioxide; CT, computerized tomography; ICP, intracranial pressure.

initially unrecordable. In 3 other patients, endotracheal intubation had failed and oxygenation was being provided by bag/mask ventilation. These latter 3 patients had unrecordable blood pressure prior to the intubation attempt.

There were 2 cardiac arrests in the group allocated to hospital intubation. Both patients had unrecordable blood pressure and cardiac arrest occurred during ambulance transport despite bag/mask ventilation with oxygen and vigorous fluid therapy. Both patients were successfully intubated during cardiopulmonary resuscitation. There were no cases of unrecognised esophageal intubation on arrival at the emergency department during this study and no patient underwent cricothyroidotomy.

After admission to hospital, both groups appeared to receive similar rates of neurosurgical interventions, including initial CT scan, urgent craniotomy (if indicated), and monitoring of intracranial pressure in the intensive care unit.

Patient Outcomes

The outcome of the patients at 6 months is shown in Table 3.. Favorable neurologic outcome was increased in the paramedic intubation patients (51%) compared with the hospital intubation patients (39%) $P = 0.046$. The median GOSe was higher in the paramedic intubation group compared with hospital intubation (5 vs. 3), however, this did not reach statistical significance ($P = 0.28$). The outcomes in 3 a priori subgroups are also shown in Table 3. There were 229 patients aged ≤60 years and in this group paramedic RSI had a favorable outcome in 62% compared with 51% on the hospital intubation group ($P = 0.094$). In the 74 patients aged >60 years, few patients in either group had a favorable outcome.

There was no difference in outcome between the groups based on initial GCS 3 to 4 compared with initial GCS 5 to 9. For patients with an initial GCS of 3, 25 of 51 (49%) of paramedic RSI patients had a favorable outcome compared with 16 of 47 (34%) of the hospital intubation patients (RR, 1.39; 95% confidence intervals, 0.89 –2.19; $P = 0.10$). There was no difference in outcome in those patients with a short transport time to hospital (10–20 minutes) compared with a longer transport time (>20 minutes).

There were 11 patients in each group who had nonsevere TBI as measured by an Abbreviated Injury Score (head) of 1 or 2 and normal CT brain scan. Of these, 6 (2 in the paramedic RSI group and 4 in the hospital intubation group) were extubated in the Emergency Department and discharged home within 24 hours.

DISCUSSION

In this prospective, randomized, controlled trial in adult patients with severe TBI, rapid sequence intubation at the scene of the injury by paramedics improved the percentage of favorable neurologic outcomes of patients at 6 months compared with patients transported to hospital without intubation. The median 6-month extended Glasgow Outcome Coma scores were higher in the paramedic intubation group, although this finding did not reach statistical significance. More patients in the paramedic intubation group had cardiac arrest prior to hospital arrival, but the overall mortality rate at hospital discharge was similar in both groups.

In the prehospital setting, endotracheal intubation has a number of potential advantages compared with no intubation: oxygenation is optimized and ventilation is controlled with the airway secured. In cities with regionalized trauma services, the patient may be stabilized at the scene and transported safely over longer distances to the most appropriate trauma hospital, thereby bypassing nontrauma designated emergency departments. On the other hand, paramedic intubation requires considerable training and could have adverse effects if intubation fails or esophageal intubation is not recognized. Also, scene time is increased which may be undesirable in patients with uncontrolled bleeding who require urgent surgery.

There have been a number of studies examining prehospital airway management in adults with traumatic brain injury, but none have been prospectively randomized, and most have examined paramedic intubation attempted without supplemental drug therapy. In a meta-analysis of studies comparing paramedic intubation with hospital intubation, there were 17 studies that enrolled a total of over 15,000

TABLE 2. Treatment and Progress*

Variable	Paramedic RSI Group (n = 160)	Hospital Intubation Group (n = 152)	P†
Prehospital			
Time at scene, min	35 ± 12	23 ± 10	<0.0005
Transport time, min	24 ± 13	23 ± 11	0.35
IV fluid, mL	1775 ± 957	1235 ± 912	<0.0005
Cardiopulmonary arrest	10 (6.3)	2 (1.3)	0.023
Emergency department			
Vital Signs on arrival			
Body temperature, °C	35.0 ± 1.5	35.6 ± 1.4	<0.0005
Systolic BP, mm Hg	128 ± 31	129 ± 38	0.68
Heart rate, beats/min	102 ± 28	96 ± 27	0.068
Oxygen saturation, %	96 ± 12.6	96 ± 4.8	0.98
First arterial blood gas			
pH	7.29 ± 0.14	7.29 ± 0.16	0.73
PaO_2, mm Hg	317 ± 180	327 ± 165	0.63
$PaCO_2$, mm Hg	46 ± 12	46 ± 11	0.63
Hemoglobin, mg/L	123 ± 25	124 ± 27	0.66
Time between ED arrival and CT brain, min	45 ± 37	52 ± 41	0.12
Discharge destination from ED, no. (%)			0.42
ICU	127 (79)	124 (82)	
Ward	11 (7.0)	10 (6.6)	
Another hospital	3 (1.9)	0	
Died	17 (11)	14 (9.2)	
Home	2 (1.3)	4 (2.6)	
Hospitalization			
Craniotomy within 6 h of ED arrival	41 (26)	32 (21)	0.31
ICP monitoring, no. (%)	73 (46)	71 (47)	0.80
ICU stay—median (IQR) h	107 (32—240)	103 (36—261)	0.74
Hospital stay—median (IQR) days	11 (5—19)	11 (3.5—21)	0.75
Survival to hospital discharge, no. (%)	107 (67)	97 (64)	0.57

*Plus-minus values are means ± SD.
†*P* values are calculated by *t* test, χ^2 or Mann-Whitney *U* test.
IQR indicates interquartile range; IV, intravenous; ED, emergency department; BP, blood pressure; ICU, intensive care unit; ICP, intracranial pressure.

TABLE 3. Outcomes at 6 Months After Injury

	Rapid Sequence Intubation Group (n = 157)	Hospital Intubation Group (n = 142)	P*
Primary outcome measure			
GOSe 1 (dead)	53	55	
GOSe 2 (vegetative state)	1	3	
GOSe 3 (severe disability-lower end)	19	20	
GOSe 4 (severe disability-upper end)	4	8	
GOSe 5 (moderate disability-lower end)	32	18	
GOSe 6 (moderate disability-upper end)	21	14	
GOSe 7 (good)	20	12	
GOSe 8 (normal)	7	12	
Median GOSe (IQR)	5 (1—6)	3 (1—6)	0.28
Secondary outcome measures			
Good neurologic outcome (GOSe 5—8)	80/157 (51%)	56/142 (39%)	0.046
Age ≤60 yr and GOSe 5—8	75/121 (62%)	54/105 (51%)	0.094
Age >60 yr and GOSe 5—8	5/35 (14%)	2/35 (6%)	0.23
Transport time ≥20 min and GOSe 5—8	48/97 (50%)	33/87 (38%)	0.12
Initial GCS 5—9 and GOSe 5—8	45/81 (57%)	34/73 (47%)	0.27
Survival at hospital discharge number	107 (67%)	97 (64%)	0.57

P values are calculated by either a χ^2 test or a Mann-Whitney *U* test.
GOSe indicates Glasgow Outcome Scale-extended; IQR interquartile range; GCS, Glasgow Coma Scale.

patients between 1985 and 2004.[5] Of these, 12 were retrospective studies, 3 were cohort studies, and 1 was a case-control study. The only controlled trial was in a pediatric population without concealment of treatment allocation. Overall, the analysis did not find any benefit from prehospital intubation after severe TBI.

Several studies have found that paramedic intubation attempts without neuromuscular blockade has a relatively low success rate and is associated with worse outcomes. For example, Stiell et al examined the outcomes of patients with major trauma following the introduction of advanced trauma life support, including paramedic intubation without neuromuscular blocking drugs and compared this approach to a historical control group who received basic airway management during prehospital care.[14] In patients with severe TBI, the survival rate with advanced life-support phase compared with the basic life-support was decreased (50.9% vs. 60.0%; $P = 0.02$). In addition, paramedic intubation success rate was only 71.8%.

There was a similar finding by Wang et al, who analyzed the data from a register on the outcomes of 4098 patients with severe TBI who received either prehospital intubation (without neuromuscular blocking drugs) or hospital intubation.[15] The mortality rate was higher in the prehospital intubation patients than hospital intubation patients (adjusted odds ratio, 3.99; 95% confidence interval, 3.21–4.93). These nonrandomized studies suggest that paramedic endotracheal intubation without the use of neuromuscular blocking drugs is associated with an increase in mortality in patients with severe TBI.

On the other hand, paramedic RSI would be expected to have a higher success rate compared with intubation without neuromuscular blockade. Only 1 previous study has examined the effects of paramedic RSI compared with hospital intubation on outcome. Davis et al, introduced paramedic RSI for patients with severe TBI into the road-based EMS in San Diego, CA.[10] The outcomes of 209 patients who underwent paramedic RSI were compared with 627 historical case-control patients who were intubated in the hospital. The mortality rate increased from 24% in the hospital intubation patients to 33% in the paramedic RSI patients ($P < 0.05$).

Paramedic intubation using RSI carries potential risks compared with transport to hospital without intubation. In our study, more patients in the paramedic intubation group suffered prehospital cardiac arrest. It is likely that the administration of sedative drugs followed by positive pressure ventilation had adverse hemodynamic consequences in patients with uncontrolled bleeding. In contrast, patients with unstable hemodynamics intubated in the hospital may have had more vigorous resuscitation, including blood transfusion than is possible in the prehospital setting. Also, when paramedic intubation failed, it is possible that oxygenation and ventilation were inadequate in some patients despite attempts at bag/mask ventilation with oxygen and this lead to subsequent cardiac arrest. It is also possible that the doses of sedative drugs administered in this study to hemodynamically unstable patients were excessive and consideration should be given to a decreasing the dose of sedation.

In our study, confirmation of endotracheal tube placement required observation of the characteristic waveform on a capnograph. Using this approach, no patient arrived at the emergency department with unrecognised esophageal intubation. This approach differs from other studies where the rate of unrecognised esophageal intubation is as high as 8%.[16]

The mechanism by which paramedic RSI may improve outcomes is unclear. The early administration of 100% oxygen would increase the partial pressure of oxygen following intubation and this hyperoxia may decrease neurologic injury.[17] Oxygen saturation was similar between the groups on hospital arrival; however, it is possible that the partial pressure of oxygen was higher during transport in the paramedic RSI group compared with patients receiving oxygen by face mask. Because arterial blood gas analysis was performed only after intubation in the hospital intubation group, the partial pressure of oxygen during ambulance transport was unknown. Controlling the minute ventilation using waveform capnography minimizes the risk of inadvertent hyperventilation or hypoventilation. In the study by Davis cited above, continuous end-tidal carbon dioxide monitoring was not used and inadvertent hyperventilation may have been a major factor leading to an increase in the mortality rate of the paramedic intubation patients.[18] Although more intravenous fluid was administered in the paramedic intubation patients, the blood pressure and hemoglobin level on arrival at the hospital were similar in both groups therefore it is likely that cerebral perfusion pressure was similar in both groups. Patient temperature was decreased in the paramedic intubation patients; however, this was less than 1°C and is unlikely to have had a measurable effect on outcome. Finally, the initial GCS may not accurately reflect the severity of neurologic injury. For example, significant chest trauma may lead to hypoventilation, hypercapnea and subsequent coma. In such patients, early intubation may improve outcome.[19]

The widespread implementation of paramedic RSI into EMS treatment protocols presents a number of challenges. Paramedic RSI is a high level skill and there is a considerable initial training cost.[20] In the present study, a 16-hour training program in RSI (for paramedics already trained in intubation) achieved an intubation success rate of 97%. This is equivalent to the intubation success rates seen in aeromedical programs[8] and physicians in the emergency department.[21] Also, management of severe TBI is a relatively uncommon event for an individual paramedic. Exposure to additional cases may be facilitated in a 2-tier EMS system that allows a smaller number of paramedics to receive additional training and maintain skills compared with a single level system.

This study has a number of limitations. It was not possible to blind paramedics and hospital physicians to treatment allocation. However, the prehospital care of all enrolled patients followed written protocols. It is very unlikely that prehospital airway management influenced major medical decisions by physicians or surgeons after admission to the hospital. In particular, the interventions that are most likely to affect neurologic outcome, such as urgent craniotomy and intracranial pressure monitoring were similar in both groups. In the Intensive Care Units, many aspects of care also followed written standardized guidelines, such as cerebral perfusion pressure management and blood glucose control.

A second limitation is that 13 of 312 patients were lost to follow-up and the majority of these were in the hospital intubation group. Despite vigorous attempts to contact these patients, all had become withdrawn from their family. It is possible that some of these missing patients in the hospital intubation group had a favorable outcome. If so, this would decrease the apparent benefit of paramedic intubation. The difference in outcomes would no longer be statistically significant whether one more patient had a positive outcome in the treatment group ($P = 0.059$) or one less in the control group ($P = 0.061$). Also, our sample size was not powered to detect uncommon but clinically important adverse events such as unrecognized esophageal intubation. Finally, some patients in our study were found to have minor head injury and it is presumed that ethanol or other drug ingestion was a factor in the initial assessment of the degree of coma. On the other hand, it appears that the severity of brain injury as measured by the Marshall CT score and Abbreviate Injury Score (head) were similar in both groups.

This study has a number of strengths. This is the first prospective, randomized controlled clinical trial of prehospital intubation in adult patients with severe head injury. The patients were well matched at enrollment and there was a high rate of paramedic compliance with the study protocol. Very few eligible patients were not enrolled, and all enrolled patients were followed to hospital discharge. There was

an intention-to-treat analysis of outcomes. Finally, the interviewer who made the assessment of outcome at 6 months was blinded to treatment allocation.

In summary, we did not find an increase in mortality rate as seen in the 1 previous study comparing paramedic RSI with hospital intubation. Instead, we found that paramedic RSI significantly improved favorable outcome at 6 months postinjury. We therefore conclude that patients with severe TBI should undergo prehospital intubation using a rapid sequence approach to increase the proportion of patients with favorable neurologic outcome at 6 months postinjury. Further studies to determine the optimal protocol for paramedic rapid sequence intubation that minimize the risk of cardiac arrest should be undertaken.

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