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Pre-hospital tracheal intubation in patients with traumatic brain injury: systematic review of current evidence

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Background. We reviewed the current evidence on the benefit and harm of pre-hospital tracheal intubation and mechanical ventilation after traumatic brain injury (TBI).

Methods. We conducted a systematic literature search up to December 2007 without language restriction to identify interventional and observational studies comparing pre-hospital intubation with other airway management (e.g. bag-valve-mask or oxygen administration) in patients with TBI. Information on study design, population, interventions, and outcomes was abstracted by two investigators and cross-checked by two others. Seventeen studies were included with data for 15 335 patients collected from 1985 to 2004. There were 12 retrospective analyses of trauma registries or hospital databases, three cohort studies, one case–control study, and one controlled trial. Using Brain Trauma Foundation classification of evidence, there were 14 class 3 studies, three class 2 studies, and no class 1 study. Six studies were of adults, five of children, and three of both; age groups were unclear in three studies. Maximum follow-up was up to 6 months or hospital discharge.

Results. In 13 studies, the unadjusted odds ratios (ORs) for an effect of pre-hospital intubation on in-hospital mortality ranged from 0.17 (favouring control interventions) to 2.43 (favouring pre-hospital intubation); adjusted ORs ranged from 0.24 to 1.42. Estimates for functional outcomes after TBI were equivocal. Three studies indicated higher risk of pneumonia associated with pre-hospital (when compared with in-hospital) intubation.

Conclusions. Overall, the available evidence did not support any benefit from pre-hospital intubation and mechanical ventilation after TBI. Additional arguments need to be taken into account, including medical and procedural aspects.

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Traumatic brain injury (TBI) is a major burden for societies.[1] Despite considerable resources being invested in acute medical care and rehabilitation, many survivors have permanent disability. In a recent cohort study, 53% of patients admitted to hospital with severe TBI died within 6 months, whereas 17% had unfavourable outcomes and only 29% favourable outcomes after 6 months.[2]

In most developed countries, pre-hospital care is performed by trained teams of out-of-hospital emergency services (OHEMS). Their principal tasks in patients with suspected TBI are, first, to provide basic or advanced life support at the scene to reduce secondary brain injury,[3–5] and secondly, to transport the patient to an adequate health-care facility within the so-called 'golden hour'.[6] At present, early tracheal intubation and mechanical ventilation are accepted standards of care in patients with severe TBI. These interventions help prevent cerebral hypoxia and increased intracranial pressure due to uncontrolled hypercapnia and resulting cerebral vasodilatation. Both these mechanisms can lead to cerebral oedema and secondary brain injury. Tracheal intubation can prevent airway obstruction and aspiration of gastric contents when

protective airway reflexes are absent. However, tracheal intubation can also be harmful. If performed in unfavourable settings and by unskilled staff, failure and resulting oxygen desaturation are more likely. Intubation on scene may increase the risk of early onset pneumonia.[7] Hyperventilation during the pre-hospital period can aggravate cerebral ischaemia and secondary brain injury with increased mortality.[8] Mechanical ventilation with uncontrolled positive pressure may reduce venous return from the cerebral circulation and increase cerebral oedema. Hence, it is controversial whether patients with severe TBI always benefit from pre-hospital intubation and mechanical ventilation. We aimed to review the current research evidence on benefit and harm of pre-hospital intubation and mechanical ventilation in patients with TBI.

Methods

Systematic literature search

Two investigators (E.v.E. and B.W.) independently conducted literature searches for relevant studies of all designs in Medline, Embase, CINAHL, and the Cochrane Library without language restrictions. We used a sensitive systematic search strategy combining the free text and thesaurus terms 'traumatic brain injury', 'head injury', or 'head trauma' with 'intubation', 'ventilation', 'pre-hospital', 'out-of-hospital', or 'emergency'. We included full publications published up to December 2007; meeting abstracts or letters were excluded. Bibliographies of retrieved reports and of relevant review articles were checked for additional articles.

We included studies if they compared patients with TBI receiving tracheal intubation and mechanical ventilation before hospital admission with those receiving other types of pre-hospital airway management. Studies were eligible, if they reported on patient-relevant endpoints such as mortality or functional outcome (e.g. Glasgow outcome scale) at the time of hospital discharge or later; studies reporting only on surrogate endpoints were excluded. Studies of patients with multiple injuries were included, if data on a well-defined subgroup of TBI patients were reported. Two reviewers (E.v.E. and B.W.) screened search results, retrieved eligible papers, and decided on study inclusion.

Data abstraction and outcome definitions

Data were abstracted by two investigators (I.H. and E.v.E.) and cross-checked by two others (B.W. and P.S.). We classified abstracted study outcomes as either benefit or harm outcomes. Benefit outcomes were reduction of mortality during the in-hospital period or later and 'good outcome' as defined by discharge destination or a scoring instrument. Harm outcomes were potential side-effects or complications of the intubation including procedure failure and ventilator-related pneumonia. Prolongation of the pre-hospital period due to field intubation was classified as harm outcome. If outcome data (e.g. for functional outcome) were dichotomized, we extracted the data as reported by the investigators. If outcomes were reported at several time points, we used data of the latest time point after injury. Disagreement on data abstraction was resolved by consensus. We assessed the relevance of each benefit and harm outcome for patients' life after TBI using elements of the GRADE methodology and classified them as 'critical', 'important', or 'not important'.[9]

Assessment of study quality

We assessed the methodological quality of included studies using the classification of evidence developed by the Brain Trauma Foundation.[10] We distinguished three classes of evidence: (i) good quality randomized controlled trial; (ii) moderate quality randomized controlled trial, good quality cohort study, or good quality case–control study; (iii) poor quality randomized controlled trial, moderate or poor quality cohort study, moderate or poor quality case–control study, case series, database- or registry-based study. Two investigators (B.W. and P.S.) independently classified each included paper; discrepancies were resolved by consulting a third reviewer (E.v.E.). We defined *a priori* two areas of potential study heterogeneity and extracted key information from each included study: (i) characteristics of study participants including age, severity of TBI assessed by Glasgow coma scale (GCS) or abbreviated injury score (AIS) for the head, or severity of all injuries assessed by injury severity score (ISS); and (ii) medical care during pre-hospital period including qualification of staff, intubation technique, rapid sequence induction (RSI), and ventilation parameters.

Data analyses

We calculated unadjusted odds ratios (ORs) and absolute risk differences (ARDs) with 95% confidence intervals (CI), if binary data were available. We defined OR >1 and ARD >0 as effects in favour of pre-hospital intubation and plotted forest plots for unadjusted effect estimates. We refrained from pooled data analyses because the designs, populations, and settings of included studies were heterogeneous and because we could not fully elucidate to what extent the same data were included in several reports for some studies. Forest and L'Abbé plots were drawn using STATA 9.

Results

Included studies

We examined the abstracts of 252 reports and read 35 articles in full. Eighteen were subsequently excluded (Fig. 1): of those, eight had a different scope[11–18] and four reported on irrelevant endpoints.[19–22] Four studies did not define distinct subgroups of TBI patients.[23–26] Two reports[19 27] were excluded because they used the same registry data as

one of the included studies.[28] We eventually included 17 articles published between 1997 and 2007[7 28–43] reporting on patient data collected between 1985 and 2004.

Thirteen studies were conducted in the USA, and four in Europe (Table 1). Of the US studies, seven were from California, and of those five from San Diego County (with overlapping periods of data collection). In total, data for 15 335 patients were analysed. The size of study groups with pre-hospital intubation ranged from 21 to 1929 (median, 268), and of the comparison groups from 25 to 2301 (median, 276). Six studies[28 30 35 38–40] were in adults, five[29 32 34 37 43] in children, and three in both[7 33 42] (Table 2). In two studies, the number of children included was unclear;[36 41] in one, age was not specified.[31]

Assessment of study quality

Study design and classification of evidence

There were 12 retrospective analyses of trauma databases, registries, or hospital files,[7 28–31 33 34 37–39 41 42] three cohort studies,[36 40 43] one case–control study,[35] and one controlled trial with treatment allocation by alternating date[32] (Table 1). Of the database studies, eight[28 31 33 34 37–39 42] used trauma registries and four[7 29 30 41] hospital files. Two cohort studies[40 43] and the case–control study[35] had a historical control group. Using the Brain Trauma Foundation classification, we regarded 14 included studies[7 28–31 33 34 36–39 41–43] as class 3 evidence and three studies as class 2 evidence (Table 1).[32 35 40] There was no class 1 evidence. In six studies,[33 36 38 39 41 42] the two reviewers' judgement on evidence classes differed and the final classification was made by consulting a third reviewer.

Patient characteristics

Patient characteristics were used for statistical adjustment of results in seven of 16 studies with mortality estimates, and in two of six studies reporting on functional outcome measured by a score. None of the included studies adjusted any estimates of harm outcomes. Overall, 13 articles included group-specific age information; the mean or median age of patients ranged from 1.0[32] to 44.8[40] yr in the intubation groups, and from 1.2[32] to 42.5[40] yr in the control groups (Table 2). In two studies,[30 36] the comparison groups differed in age by 5 yr or more; none adjusted for age. In 10 studies with group-specific information on neurological status, the mean or median initial GCS ranged from 3.0[31 33] to 5.2[30] in the intubation groups, and from 4.4[28] to 8.0[7 28] in the control groups. In four studies,[7 28 29 40] the groups differed by one GCS point or more. One study adjusted for GCS,[40] another[29] did not. Adjustment for GCS was unclear in one study[28] and was not reported for the TBI subgroup in another.[7] In 10 studies with group-specific information on the severity of TBI, the mean or median AIS of head region ranged from 3.2[7] to 5.1[29] in the intubation groups, and from 2.7[7] to 5.0[31] in the control groups. The maximum difference between the study groups in a single study was 0.5 AIS points. Two studies[30 43] were restricted to isolated TBI. In 10 studies with group-specific information on the overall severity of injury, the mean or median ISS ranged from 20.1[36] to 39.8[29] in the intubation groups, and from 18[7] to 35[31] in the control groups. In three of these studies,[7 28 29] the difference between the groups was 5 ISS points or more. Adjustment for ISS was not done in one study,[29] unclear in another,[28] and not reported for the subgroup of head-injured patients in yet another study.[7]

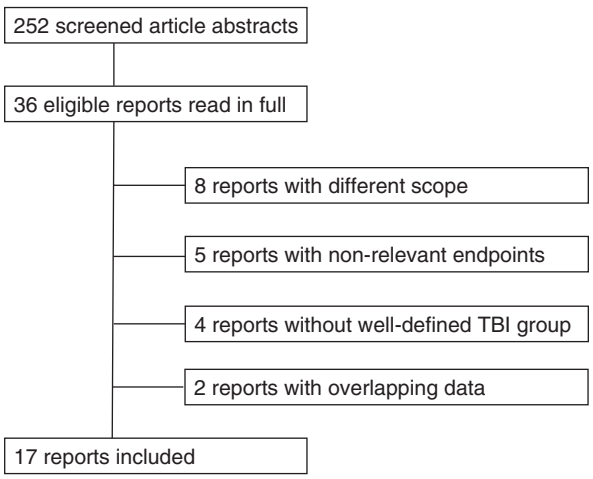

Fig 1 Flow chart of study selection.

Pre-hospital intubation and mechanical ventilation

In four articles,[32 35 36 40] pre-hospital intubation and ventilation protocols were described in detail. In two studies, paramedics received specific training within the study's framework for 6[32] and 8 h,[35] respectively. RSI was performed in all field-intubated patients in four studies[30 35 36 40] and partly in three studies.[29 31 38] In one study,[33] patients were intubated without prior medication. The remaining nine reports[7 28 32 34 37 39 41–43] did not mention medication for intubation.

Four studies specified the pre-hospital airways management in the control group as bag-valve-mask ventilation[32 34 35] or spontaneous breathing.[41] None provided data on the inspired oxygen concentration used. The pre-hospital airway management of control groups was unclear in the remaining 13 studies. However, five studies[7 30 36–38] mentioned that patients were intubated at hospital arrival. Two studies[29 37] distinguished between intubation in trauma and non-trauma centre hospitals, and another[33] between successful and attempted intubation.

Two study reports[35 43] described pre-defined goals for mechanical ventilation after successful intubation for all or part of included patients, but none reported on the chosen inspired oxygen fraction level. Five studies[32 35 36 40 41] reported on measured respiratory parameters: three[36 40 41]

Table 1 Characteristics of included studies. ALS, advanced life support; BLS, basic life support; ED, emergency department; RSI, rapid sequence intubation. *On the basis of the number of study participants with TBI evaluated for in-hospital mortality. †Using criteria of the Brain Trauma Foundation.[10] ‡Participants evaluated for pneumonia. §Participants evaluated for ICU and 90 day mortality

Study	Design	Period of data collection	Study size*	Study region	Type of admitting hospital	Study interventions	Class of evidence†
Suominen and colleagues[29]	Database study	January 1985 to December 1994	59	Province of Uusimaa (Finland)	1 trauma centre (level 1)	Pre-hospital *vs* intubation in ED of regional hospital *vs* intubation in ED of trauma centre	3
Sloane and colleagues[30]	Database study	Pre-hospital RSI: January 1988 to December 1995; RSI in ED: January 1992 to December 1995	75	San Diego County, CA (USA)	1 trauma centre (level 1)	Pre-hospital *vs* RSI in ED	3
Winchell and Hoyt[31]	Database study	January 1991 to December 1995	671	San Diego County, CA (USA)	6 trauma centres	Pre-hospital intubation *vs* other airway management (unclear if aeromedical transport is included)	3
Gausche and colleagues[32]	Controlled clinical trial with treatment allocation alternating by day	March 1994 to January 1997	61	Los Angeles and Orange counties, CA (USA)	Los Angeles: 9 paediatric/13 adult trauma centres; Orange: several paramedic+tertiary care centres	Pre-hospital intubation *vs* bag-valve-mask	2
Murray and colleagues[33]	Database study	January 1995 to December 1997	795	Los Angeles County, CA (USA)	13 trauma centres	Pre-hospital intubation without medication *vs* other; subgroup with failed pre-hospital intubation	3
Cooper and colleagues[34]	Database study	Until October 1999	578	National Pediatric Trauma Registry (USA)	Not available	Pre-hospital intubation *vs* bag-valve-mask	3
Davis and colleagues[35]	Case–control study (historical controls)	November 1998 to November 2000	670	San Diego County, CA (USA)	5 trauma centres	RSI *vs* other	2
Bochicchio and colleagues[36]	Cohort study	August 2000 to August 2001	191	Maryland (USA)	1 trauma centre (level 1)	Pre-hospital *vs* ED intubation	3
DiRusso and colleagues[37]	Database study	April 1994 to January 2002	1018	National Pediatric Trauma Registry (USA)	90 paediatric hospitals or trauma centres	Pre-hospital *vs* intubation in non-trauma centre *vs* intubation in trauma centre	3
Wang and colleagues[38]	Database study	January 2000 to December 2002	4098	Pennsylvania (USA)	25 adult trauma centres	Pre-hospital *vs* ED intubation	3
Eckert and colleagues[7]	Database study	July 1998 to December 2002	363 ‡	Illinois (USA)	1 trauma centre (level 1)	Field intubation *vs* ED intubation	3
Davis and colleagues[39]	Database study	January 1987 to December 2003	2243	San Diego County, CA (USA)	5 trauma centres	Pre-hospital intubation+air transport *vs* ground transport+ED intubation	3
Davis and colleagues[28]	Database study	January 1987 to December 2003	2813	San Diego County, CA (USA)	5 trauma centres	Pre-hospital *vs* ED intubation	3
Klemen and Grmec[40]	Cohort study (historical controls)	January 1998 to January 2004	124	Maribor (Slovenia)	1 trauma centre	ALS incl. pre-hospital RSI by emergency physician *vs* emergency medical technician care	2
Lenartova L and colleagues[41]	Database study	October 1999 to March 2004	393§	Austria	5 trauma centres (level 1)	Pre-hospital intubation *vs* no pre-hospital intubation	3
Hartl and colleagues[42]	Database study	June 2000 to December 2004	1123	New York State (USA)	5–22 trauma centres (level 1 or 2)	ALS incl. intubation *vs* BLS	3
Stanic-Canji and colleagues[43]	Cohort study (historical controls)	Not reported	60	Serbia	Not reported	Adequate pre-hospital resuscitation (incl. intubation+controlled ventilation as one of the seven criteria) *vs* inadequate resuscitation	3

Table 2 Patient characteristics. AIS, abbreviated injury score; ALS, advanced life support; CPR, cardiopulmonary resuscitation; ED, emergency department; GCS, Glasgow coma scale; IQR, inter-quartile range; ISS, injury severity score; MTOS, Major Trauma Outcome Study; NA, not available; RHISS, relative head injury severity scale; RSI, rapid sequence intubation; TBI, traumatic brain injury. *Mean (SD or range) if not indicated otherwise. †Data of all study participants. ‡GCS was 3 in 75 (93%) patients. §GCS was 3 in 443 (62%) patients. ¶Calculated from published data

Study	Population	Inclusion criteria; definition of study group with TBI	Exclusion criteria	Age (yr)*		Glasgow coma scale*		Head abbreviated injury score*		Injury severity score*		Respiratory parameters*	
				Pre-hospital intubation	Control intervention	Pre-hospital intubation	Control intervention	Pre-hospital intubation	Control intervention	Pre-hospital intubation	Control intervention	Pre-hospital intubation	Control intervention
Suominen and colleagues[29]	Paediatric	Head/neck AIS 4 or more, age <16 yr, required intensive care, or died before admission	Incomplete information on intubation timing, arrival at hospital >150 min after accident	11.2 (5.0–15.8)	10.2 (0.2–15.9)	4.3 (3–11)	6.6 (4–12)	5.1 (5–6)	4.8 (4–5)	39.8 (25–75)	31.4 (16–50)	NA	NA
Sloane and colleagues[30]	Adult	Isolated head injury GCS 8 or less, ISS 9 or more, head/neck AIS 3 or more, all other AIS 3 or less	Interfacility transfers, intubation before arrival of aeromedical crews, incomplete records nasotracheal intubation, non-RSI, cricothyrotomy	26.2	36.2	5.2	5.8	4.8	4.7	31.4	29.0	NA	NA
Winchell and Hoyt[31]	Age not defined	MTOS criteria, GCS 8 or less, blunt injury, subgroup with head/neck AIS 4 or more (severe head injury)	NA	33.3	34.3	Mean: 4.5; median: 3	Mean: 4.0; median: 3	Mean: 4.6; median: 5	Mean: 4.7; median: 5	Mean: 33; median: 29	Mean: 35; median: 30	NA	NA
Gausche and colleagues[32]	Paediatric	Age 12 yr or less or weight 40 kg or less; subgroup with closed/open head trauma with non-purposeful response or no response to pain	Incomplete records	Median: 1 (IQR 0.25–3.3)†	Median: 1.2 (IQR 0–3.5)†	NA	NA	NA	NA	NA	NA	Median oxygen saturation: 97% (IQR: 93–100)	Median oxygen saturation: 98% (IQR: 92–100)
Murray and colleagues[33]	Paediatric+ adult	Field GCS 8 or less and AIS head 3 or more	NA	34	34	Median: 3‡	Median: 3§	4.4¶	4.6¶	29.6	26.7	NA	NA
Cooper and colleagues[34]	Paediatric	Children with head injury (AIS >3)	NA	Age groups (yr): <1: 4%; 1–4: 21%; 5–9: 25%; 10–14: 32%; 15+: 18%	Age groups (yr): <1: 5%; 1–4: 35%; 5–9: 31%; 10–14: 18%; 15+: 10%	NA	NA	NA	NA	ISS groups: 1–9: 0%; 10–19: 11%; 20–75: 80%; NA: 9%	ISS groups: 1–9: 0%; 10–19: 10%; 20–75: 85%; NA: 5%	NA	NA

Continued

Table 2. *Continued*

Study	Population	Inclusion criteria; definition of study group with TBI	Exclusion criteria	Age (yr)*		Glasgow coma scale*		Head abbreviated injury score*		Injury severity score*		Respiratory parameters*	
				Pre-hospital intubation	Control intervention	Pre-hospital intubation	Control intervention	Pre-hospital intubation	Control intervention	Pre-hospital intubation	Control intervention	Pre-hospital intubation	Control intervention
Davis and colleagues[35]	Adult	18 yr or older, major trauma, GCS 3–8, transport 10 min or more, intubation without RSI impossible	No i.v. access, CPR before RSI, intubation impossible after RSI, head/neck AIS <2, neck injury, MTOS criteria not fulfilled, survival <30 min after accident or ED arrival	37.1	36.8	NA	NA	3.91	3.92	27.6	26.3	Arterial blood gas at hospital arrival: pH: 7.36; P_{O_2}: 315 mm Hg; P_{CO_2}: 34.9 mm Hg	Arterial blood gas at hospital arrival: pH: 7.36; P_{O_2}: 216 mm Hg; P_{CO_2}: 38.3 mm Hg
Bochicchio and colleagues[36]	Adult, unclear if children included	Trauma, GCS <9, AIS head <2	Survival <48 h, failed field intubation, long field extrication, interhospital transfer	35 (21)	40 (15)	4 (0.8)	4.4 (2.1)	4.9 (0.7)	4.5 (0.9)	20.1 (8)	19.2 (9)	Field O_2 sat.: 89% (7)	91% (6)
DiRusso and colleagues[37]	Paediatric	Age <20 yr subgroup with severe head injury (defined by RHISS=3)	NA	9.1 (5.4)	Intubation in: trauma centre 8.0 (5.4); non-trauma centre 7.05 (5.2)	NA	NA	NA	NA	NA	NA	NA	NA
Wang and colleagues[38]	Adult	Age >18 yr head/neck AIS 3 or more	Interhospital transfer, pre-hospital care not by ALS team, intubation after ED stay or no intubation	NA	NA	NA	NA	4.4¶	4.1¶	NA	NA	NA	NA
Eckert and colleagues[7]	Paediatric+ adult	Patient with trauma requiring urgent airway management; subgroup with head injury	Burn injury; death within 48 h	36 (20)†	35 (21)†	4 (2)†	8 (5)†	3.2 (1.3)	2.7 (1.8)	26 (7)†	18 (14)†	Base deficit (at admission): −5 (6)	−6 (3)
Davis and colleagues[39]	Adult	MTOS criteria, head/neck AIS >3	Neck injury, incomplete data, interhospital transport	33.0	37.5	4.1	4.6	4.42	4.42	32.9	31.2	NA	NA
Davis and colleagues[28]	Adult	MTOS criteria, head/neck AIS >3	Neck injury	35.3	37.6	4.4	8.0	4.6	4.2	36.6	28.3	NA	NA
Lenartova and colleagues[41]	Adult (few children included)	Initial GCS 8 or less or deteriorating to GCS 8 or less within first 48 h	Patients who died at scene, during transport, or immediately after ED admission	48.9 (20.8)		5.6 (2.9)		NA		27.0 (12.7)		Pre-hospital oxygen saturation: <90%: 7.2%; 90–95%: 13.6%; 96–97%: 31.5%; 98–100%: 47.7%	

Hartl and colleagues[42]	Paediatric+ adult	Arrival at trauma centre within 24 h; GCS <9	GCS motor score=6 on any day; subarachnoid haemorrhage secondary to aneurysm or stroke; GCS=3 with pupils bilaterally fixed	36.0 (20.6); range: 0.1–93.7		GCS score: 3–5 in 53.7%, 6–8 in 33.3%, >9 in 13.0%	NA	NA		NA	
Klemen and Grmec[40]	Adult	GCS <9, ISS >15, AIS head >3	NA	44.8 (23.6); range: 18–86	42.5 (21.3); range: 18–82	Median: 5; IQR: 3–8	Median: 6; IQR: 4–8	NA	NA	Median: 24; IQR: 16–26	Median: 23; IQR: 17–25	Oxygen saturation: initial: 84% (10); Hosp. arrival: 96% (3)	86% (11); 89% (8)
Stanic-Canji and colleagues[43]	Paediatric	Isolated craniocerebral injuries not requiring surgical treatment, age ≤17 yr, GCS <8	NA	10.4	11.2	5	5.17	NA	NA	NA	NA	NA	NA

on oxygen saturation at baseline or time of hospital admission or both; one[32] on median oxygen saturation; and one[35] on arterial blood gases measured at hospital admission. Hyperventilation was described in two studies: 6% of intubated patients were hyperventilated in one study[41] and all patients with signs of clinical deterioration in another.[40] No study mentioned hypoventilation.

Relevance of study outcomes

We assessed the relevance of the reported outcomes for our research question.[9] Most studies reported on mortality during hospital stay. For mortality estimates, only one study[41] used a fixed time interval of 90 days, which exceeded an average length of hospital stay for TBI. We deemed 'in-hospital mortality' a critical outcome. After current recommendations on TBI research,[44] we considered functional outcome another critical outcome, if measured by validated scoring instruments 6 months or more after the injury. Only one study[40] used such an endpoint. We regarded functional outcome at the time of hospital discharge as an important (but not critical) outcome. Discharge destination was not deemed important because it is not a valid surrogate of patients' outcome.

Harm outcomes related to pre-hospital airway management were deemed critical outcomes. However, the studies used various definitions for harm outcomes and most of them reported sparse data only.

Summary of reported study outcomes

Reduction of mortality

Fifteen studies reported mortality during the in-hospital period. None provided information on the actual length of survival after injury. In 13 studies, the unadjusted ORs for an effect of pre-hospital intubation on in-hospital mortality ranged from 0.17 (95% CI: 0.10–0.31)[33] to 2.43 (95% CI: 1.78–3.33)[31] (Fig. 2, Table 3). The absolute differences for in-hospital mortality risk ranged from −21.8%[31] to 38.2%[33] (Table 3) and the corresponding event rates from 14.3%[30] to 81.5%[33] for pre-hospital intubation and from 12.4%[36] to 68.0%[32] for other airway management (Fig. 3). The point estimates of eight studies[28 29 32 33 35–38] favoured other airway management and of five studies[30 31 34 39 40] pre-hospital intubation. Seven studies[28 33 35 38–40 42] reported adjusted ORs for in-hospital mortality estimates ranging from 0.24 (95% CI: 0.11–0.49)[33] to 1.42 (95% CI: 1.13–1.78)[39] (Table 3). In most of these studies, the selected confounding factors included age, sex, and at least one measure of injury severity. In two studies, it was unclear which factors were selected for adjustment.[28 35]

One study[40] reported 1 and 24 h mortality. At both time points, pre-hospital advanced life support and rapid sequence intubation was superior to standard pre-hospital care without intubation (Table 3; Fig. 2). Another study[41] reported mortality in the intensive care unit and after

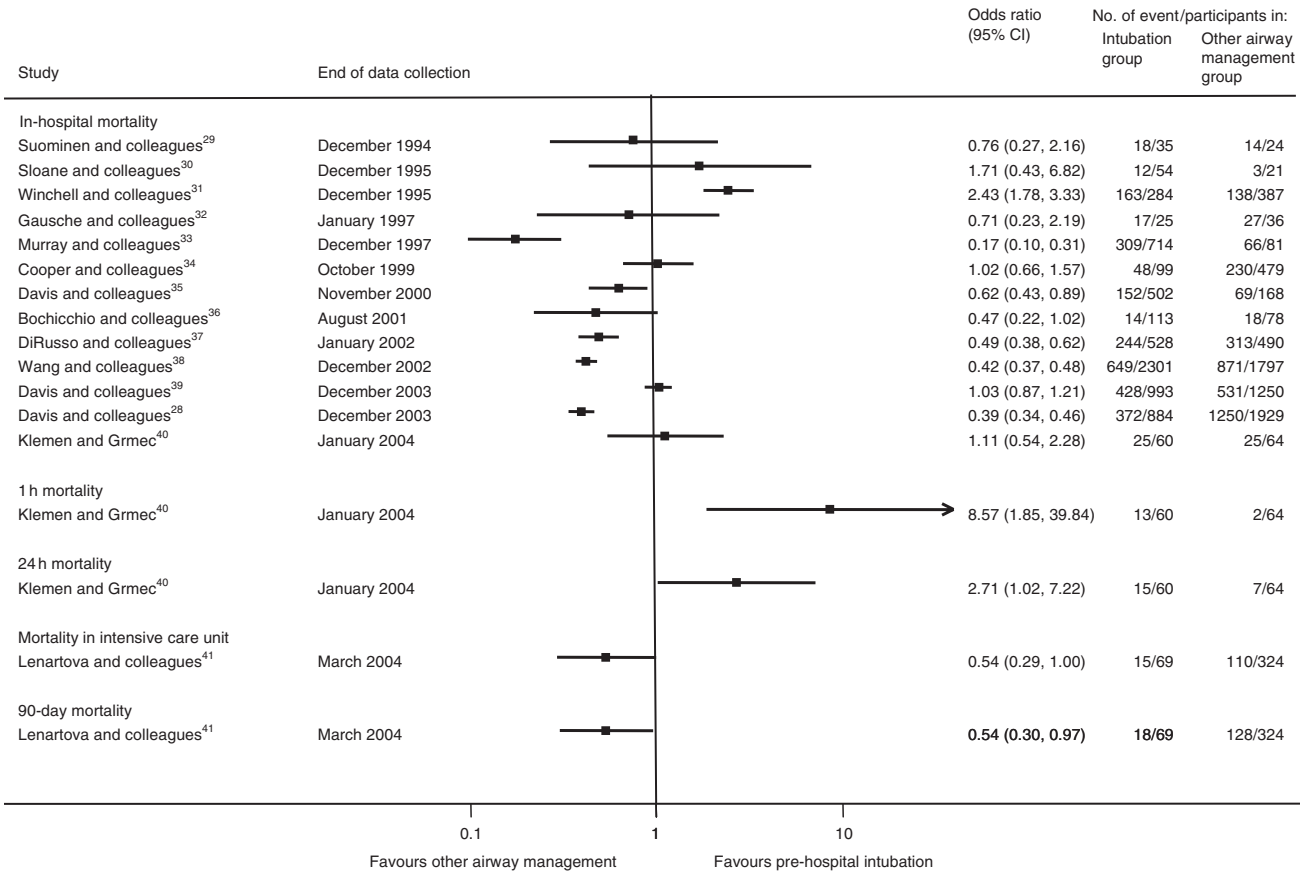

Fig 2 Overview of unadjusted estimates of mortality.

90 days. At both time points, the control intervention was superior.

Functional outcome

Five studies[3 30 31 37 38] reported functional outcome defined by destination at hospital discharge (Table 3). In two studies,[31 37] good outcome was defined as discharge to home, and in three studies[30 35 38] as discharge to home, rehabilitation, psychiatric facility or jail, or signing out against medical advice. None of these studies included data on the time elapsed between trauma and hospital discharge. Three studies[35 37 38] reported better outcome with control interventions, and one study[31] with pre-hospital intubation (Table 3, Fig. 4). One small study[30] was inconclusive. In two studies, estimates were adjusted for confounding factors;[35 38] both were in favour of the control interventions (Table 3).

Six studies[32 34 37 38 40 41] used scoring instruments for functional outcome. 'Good outcome' was defined as functional independence measure (FIM) level of 5–7;[34] 'normal' FIM score[37] (without definition of 'normal'); modified Pediatric Cerebral Performance Category Scale indicating either normal status, no change from baseline, or mild disability,[32] favourable final outcome (i.e. good recovery or moderate disability)[41] or functional impairment score of 0–5 (i.e. mild impairment) on a scale ranging from 0 to 15.[38] In two studies,[34 40] pre-hospital intubation was superior with regard to functional outcome by score; in two others,[37 38] the control groups fared better (Fig. 4). Two studies[32 41] were inconclusive. One study[37] stratified by severity of head injury and another[38] used propensity scores for adjustment. In both, adjusted functional outcomes were in favour of the control interventions. One[37] included only percentage data for functional outcomes (not shown in Fig. 4).

Harm outcomes

Seven[7 30 32–36] studies reported on harmful effects of pre-hospital intubation or other airway management (Table 4). In five studies,[30 32–35] the frequency of different procedure failures or complications during airway management were reported. With pre-hospital intubation, intubation failure or complication rates ranged from 2.1%[30] to 41.1%[35] (Table 4). Two reports[30 34] included absolute numbers of intubation failures in the pre-hospital and in-hospital period; study results were inconclusive (Fig. 5). Three studies[7 30 36] reported on pneumonia after pre-hospital or in-hospital intubation; it was the primary study outcome in one study.[7] Diagnostic criteria were reported in two,[7 36] but unclear in another.[30] Pre-hospital intubation was

Table 3 Overview of benefit outcomes. AIS, abbreviated injury score; GCS, Glasgow coma scale; ISS, Injury severity score; NA, not available; RHISS, Relative Head Injury Severity scale. *OR >1 indicates better outcome with pre-hospital intubation. †Comparison groups combined. ‡Calculated from reported data. §Extracted from published graph. ¶Based on all participants. +Only in survivors

Study	Number of outcome events/patients with pre-hospital intubation	Number of outcome events/patients with control intervention	Unadjusted odds ratio (95% CI)*	Absolute risk difference	Factors used for adjusting statistical models	Adjusted odds ratio (95% CI)*
In-hospital mortality						
Suominen and colleagues[29]	14/24 (58.3%)	Intubated at regional hospital: 12/13 (92.3%); intubated at trauma centre: 6/22 (27.3%); combined: 18/35 (51.4%)	1.32 (0.44–4.31)†	6.9%†	None	
Sloane and colleagues[30]	3/21 (14.3%)	12/54 (22.2%)	1.71 (0.39–10.53)	−7.9%	None	
Winchell and Hoyt[31]	138/387 (35.6%)	163/284 (57.4%)	2.43 (1.75–3.37)	−21.8%	None	
Gausche and colleagues[32]	27/36 (75.0%)	17/25 (68.0%)	0.71 (0.23–2.19)	7.0%	None	
Murray and colleagues[33]	66/81 (81.5%)	309/714 (43.3%)	0.17 (0.09–0.31)	38.2%	Gender, GCS, head AIS, ISS, transport mode, assoc. injuries, mechanism of injury	0.24 (0.11–0.49)‡
Cooper and colleagues[34]	230/479 (48.0%)	48/99 (48.5%)	1.02 (0.66–1.57)	−0.5%	None	
Davis and colleagues[35]	69/168 (41.1%)	152/502 (30.3%)	0.62 (0.43–0.91)	10.8%	Total of 15 matching parameters mentioned in two different paragraphs of article	0.66 (0.44–0.93)‡
Bochicchio and colleagues[36]	18/78 (23.0%)	14/113 (12.4%)	0.47 (0.22–1.02)	10.6%	None	
DiRusso and colleagues[37]	313/490 (63.9%)	Intubated at non-trauma centre: 128/254 (50.5%); intubated at trauma centre: 116/274 (42.3%); combined: 244/528 (46.2%)	0.49 (0.37–0.63)†	17.7%†	None (for subgroup with head injury)	
Wang and colleagues[38]	871/1797 (48.5%)	649/2301 (28.2%)	0.42 (0.37–0.48)	20.3%	Age, sex, head/neck AIS, systolic arterial pressure on admission, penetrating/blunt injury, mode of transport, neuromuscular blocking agents, propensity score for pre-existing medical conditions, in-hospital course, and social variables	0.25 (0.20–0.35)
Davis and colleagues[39]	531/1250 (42.5%)	428/993 (43.1%)	1.03 (0.87–1.21)	−0.6%	Age, sex, mechanism, preadmission hypotension, head AIS, ISS, initial GCS	1.42 (1.13–1.78)
Davis and colleagues[28]	1250/1929 (64.8%)	372/884 (42.1%)	0.39 (0.34–0.46)	22.7%	Choice of factors for adjustment is unclear	0.70 (0.57–0.86)
Klemen and Grmec[40]	25/64 (39.1%)	25/60 (41.7%)	1.11 (0.51–2.43)	−2.6%	Age, gender, mechanism of injury, GCS, ISS, initial Sa_{O_2}, syst. arterial pressure	3.85 (1.84–6.38)
Hartl and colleagues[42]	Total number: 441. Number of deceased patients not reported	Total number: 682. Number of deceased patients not reported	Not reported	Not reported	Hypotension status on day 1, age (less/more than 60 yr), pupil status on day 1 (normal/abnormal), initial GCS	0.82 (0.59–1.14)
Stanic-Canji and colleagues[43]	Intubated patients: n=31	Not intubated patients: n=29	Not reported	Not reported		

Continued

Table 3. *Continued*

Study	Number of outcome events/patients with pre-hospital intubation	Number of outcome events/patients with control intervention	Unadjusted odds ratio (95% CI)*	Absolute risk difference	Factors used for adjusting statistical models	Adjusted odds ratio (95% CI)*
Other mortality time points						
Klemen and Grmec[40]	1 h mortality: 2/64 (3.1%)	13/60 (21.7%)	8.57 (1.78–80.67)	−18.6%	Age, gender, mechanism of injury, GCS, ISS, initial Sa_{O_2}, syst. arterial pressure	2.24 (1.78–2.91)
Klemen and Grmec[40]	24 h mortality: 7/64 (10.9%)	15/60 (25.0%)	2.71 (0.94–8.51)	−14.1%	Age, gender, mechanism of injury, GCS, ISS, initial Sa_{O_2}, syst. arterial pressure	2.61 (1.83–3.85)
Lenartova and colleagues[41]	Mortality in ICU: 110/324 (34.0%)	15/69 (21.7%)	0.54 (0.30–0.97)	12.3%	None	
Lenartova and colleagues[41]	90 day mortality: 128/324 (39.5%)	18/69 (26.1%)	0.54 (0.29–1.00)	13.4%	None	
Good outcome (defined by discharge destination)						
Sloane and colleagues[30]	8/21 (38.1%)	20/54 (37.0%)	1.04 (0.32–3.30)	1.1%	None	
Winchell and Hoyt[31]	101/387 (26.1%)	48/284 (16.9%)	1.74 (1.16–2.61)	9.2%	None	
Davis and colleagues[36]	63/168 (37.5%)	247/502 (49.3%)	0.62 (0.43–0.90)[‡]	−11.8%	Total of 15 matching parameters mentioned in two different paragraphs of article	0.62 (0.43–0.90)
DiRusso and colleagues[37]	20%[§]	25%[†,§]			Stratification by RHISS; only data for severe head injury were extracted	
Wang and colleagues[38]	739/1797 (41.1%)	1344/2301 (58.4%)	0.50 (0.44–0.56)[¶]	−17.3%	Age, sex, head/neck AIS, systolic arterial pressure on admission, penetrating/blunt injury, mode of transport, neuromuscular blocking agents, propensity score for pre-existing medical conditions, in-hospital course, and social variables	0.62 (0.44–0.87)[‡,+]
Good outcome (defined by scoring instrument)						
Gausche and colleagues[32]	Paediatric cerebral performance category scale (no/mild disability; no change from baseline): 4/36 (11.1%)	2/25 (8.0%)	1.44 (0.24–8.52)	3.1%	None	
Cooper and colleagues[34]	Functional independence measure (5 or more): 49/163 (30.0%)	2/23 (8.7%)	4.51 (1.03–40.95)	21.3%	None	
DiRusso and colleagues[37]	Normal FIM score: 10%[§]	20%[†,§]			Stratification by RHISS	
Wang and colleagues[38]	Functional impairment score (0–5=mild): 288/1797 (16.0%)	761/2301 (33.0%)	0.39 (0.33–0.45)	−17%	Age, sex, head/neck AIS, systolic arterial pressure on admission, penetrating/blunt injury, mode of transport, neuromuscular blocking agents, propensity score for pre-existing medical conditions, in-hospital course, and social variables	0.52 (0.38-0.71)[‡,+]
Klemen and Grmec[40]	GOS 4 or 5: 34/64 (53.1%)	21/60 (35%)	1.57 (0.70–3.53)	18.1%	None	
Lenartova and colleagues[41]	'Favourable outcome': 112/324 (34.6%)	28/69 (40.6%)	0.77 (0.44–1.37)	−6.0%	None	

consistently associated with increased odds of pneumonia (Table 4, Fig. 5). One study[35] reported that inadvertent hyperventilation was associated with pre-hospital intubation. A paediatric study[32] included data on complications of airway management for all patients (including those with other injury) and showed no difference between study groups. Seven studies[29 30 32 35–37 40] included data on pre-hospital delays (Table 4). The mean or median time on scene with pre-hospital intubation ranged from 11[32] to 29 min,[40] and with control interventions from 9[32] to 27 min.[40] In three studies,[30 32 35] the time on scene was significantly longer with pre-hospital intubation.

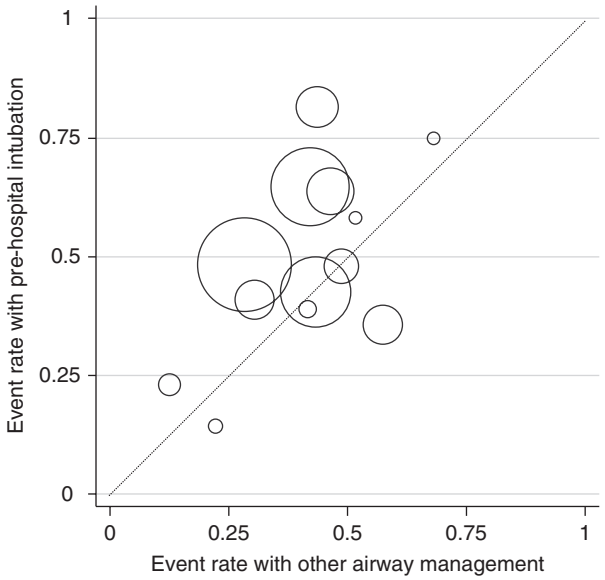

Fig 3 In-hospital mortality rates, L'Abbé plot of 13 included studies. Size of circles is proportional to study size.

Discussion

We reviewed the current research evidence on the efficacy and harm of pre-hospital intubation and mechanical ventilation from more than 15 000 included TBI patients. The overall strength of this evidence was low. In many studies, we found a lack of statistical adjustment for important confounding factors and of reported detail about control interventions and harm outcomes. The reports did not show any consistent beneficial or harmful effect of pre-hospital intubation on critical outcomes.

Limitations of original studies

None of the included studies used proper randomization and therefore could not be classified as class 1 evidence. Three of 17 studies were class 2 and 14 studies class 3 evidence. It was unclear to what extent the included studies were susceptible to biases and overestimation of effects. Information on drop-outs was provided only rarely and, consequently, attrition could not be assessed. Most studies were based on already existing data sets such as trauma

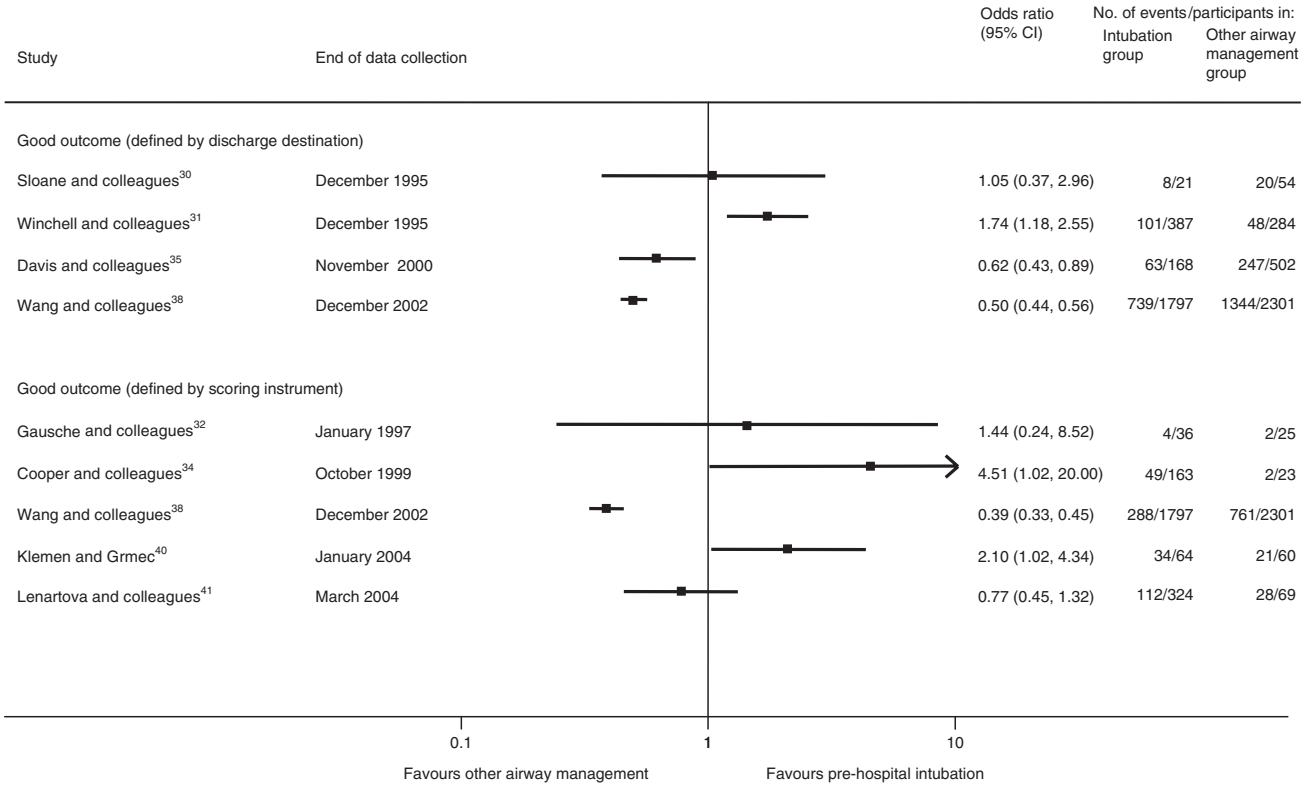

Fig 4 Overview of unadjusted estimates of functional outcome.

Table 4 Overview of harm outcomes. IQR, inter-quartile range. NA, not available; SD, standard deviation. *Statistically significant ($P<0.05$) differences between study groups. [†]OR >1 indicates better outcome with pre-hospital intubation. [‡]In all trauma patients. [§]All values are means (range) if not indicated otherwise. [¶]Statistically significant difference to intubation at regional hospital. [+]Data extracted from the graph. [#]Only patients intubated in trauma centre

Study	Outcome event	Number of patients with event/ overall number in pre-hospital intubation group	Number of patients with event/ overall number in comparison group	Unadjusted odds ratio (95% CI)[†]	Absolute risk difference	Factors used for statistical adjustment
Procedure failure						
Sloane and colleagues[30]	Multiple intubation attempts	8/46 (17.4%)	36/263 (13.7%)	0.75 (0.31–2.02)	3.7%	None
	Intubation failure	1/47 (2.1%)	4/267 (1.5%)	0.71 (0.69–35.94)	0.6%	None
Gausche and colleagues[32‡]	Main stem intubation	18%	NA			None
	Recognized/unrecognized dislodgement	8/6%				
	Oesophageal intubation	2%				
	Tube of incorrect size	24%				
Murray and colleagues[33]	Unsuccessful intubation	57/852 (6%)	NA			None
Cooper and colleagues[34]	Procedure or equipment failure or complications	38/479 (7.9%)	8/99 (8.1%)	1.02 (0.40–2.32)	−0.2%	None
Davis and colleagues[35]	Multiple intubation attempts	86/209 (41.1%)	NA			None
Pneumonia						
Sloane and colleagues[30]		14/47 (29.8%)	26/267 (9.7%)	0.25 (0.11–0.59)	21.1%	None
Bochicchio and colleagues[36]		38/78 (48.7%)	36/113 (31.8%)	0.49 (0.26–0.93)	16.9%	None
Eckert and colleagues[7]		30/87 (34.5%)	72/276 (26.1%)	0.67 (0.39–1.17)	8.4%	None for subgroup with head injury
Other harm outcomes						
Gausche and colleagues[32‡]	Complication of airway management incl. gastric distension, vomiting, aspiration, oral/ airway trauma	176/363 (48.5%)	170/364 (46.7%)	0.93 (0.69–1.26)	1.8%	None
Davis and colleagues[36]	Inadvertent hyperventilation	32/209 (15.3%)	50/627 (8.0%)	0.48 (0.29–0.80)	7.3%	None
Prolongation of pre-hospital period (min)[§]						
Suominen and colleagues[29]	Call to arrival in level 1 trauma centre	56.4 (20.0–143-0)*,[¶]	Intubation at regional hospital: 111.6 (55–150), at level 1 trauma centre 45.0 (16–108)			None
Sloane and colleagues[30]	Time on scene	25.7*	14.2			None
	Transport time	10.5*	13.3			
Gausche and colleagues[32‡]	Time on scene	Median 11 (IQR 7–16)*	Median 9 (IQR 5–13)			None
	Transport time	Median 6 (IQR 4–9)	Median 6 (IQR 4–8)			
	Total time	Median 23 (IQR 18–29)*	Median 20 (IQR 16–26)			
Davis and colleagues[35]	Time on scene	22.8*	16.4			None
Bochicchio and colleagues[36,+]	Dispatch of team until hospital arrival (ground/air transport)	46/52*	30/37			None
DiRusso and colleagues[37]	Time of incident until hospital arrival	119*	88[#]			None
Klemen and Grmec[40]	Time on scene	29 (SD 8)	27 (SD 9)			None

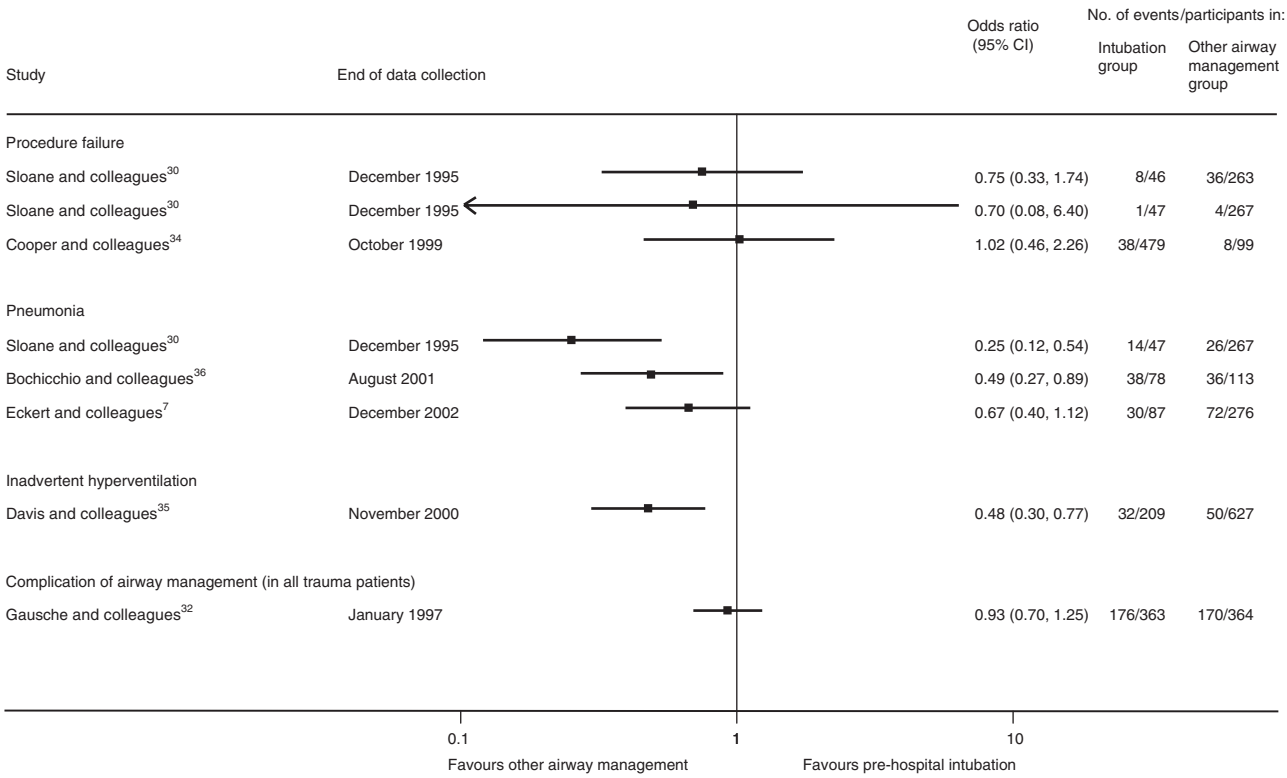

Fig 5 Overview of unadjusted estimates of harm outcomes.

registries. Although such studies are often larger than experimental studies, their internal validity is often limited. Six of the studies included had <200 participants with TBI. Clearly, the small sample size limits the validity of these studies. Some included studies had long durations of data collection or used historical controls. Differences in observed effects may be due to changes in clinical practice and organization of health services over time rather than the interventions compared. Further, multi-purpose data sets often lack information on important confounders and patient-relevant long-term outcomes. Most included studies reported in-hospital mortality, but only a few on other important outcomes (e.g. functional outcome after 6 months). In some studies, data on confounding factors were collected but not used for statistical adjustment. For instance, in two studies, there was a difference in initial GCS between the intubation and the control group that was not accounted for in the analyses.[7 29] Other studies were too small to allow multivariate analyses. The control groups of most studies were not sufficiently described. For instance, airway management before hospital admission was often not described for studies with intubation in the emergency department as control intervention. The data suggested that the comparison groups differed in several aspects, such as injury severity. Other important study information was given only sparsely including intubation failure rates, skills and training for intubation, monitoring of mechanical ventilation on the accident scene and during transport, and institutional characteristics including TBI patient volume of trauma centres. Some studies used outcomes with short follow-up times or variable definition (e.g. hospital discharge). However, it is inappropriate to evaluate functional outcomes or quality of life earlier than 6 months after injury.[44]

Strengths and limitations of our review

We used rigorous review methods to search and assess the relevant literature. Compared with earlier reviews,[45 46] our literature search was more extensive and the inclusion criteria were stricter. For instance, we excluded studies on pre-hospital intubation and neuromuscular blocking[16] and those without well-defined groups of TBI patients.[23–26] However, we may have missed eligible studies, in particular if they were not indexed in the used literature databases or not published in full. Further, it is possible that some studies, for example, those with inconclusive results, were not published or that other reporting biases occurred. For instance, we observed that most investigations were performed in the USA, and most of them in California, while other countries were under-represented. However, we refrained from a more formal investigation of possible biases given that pooled analyses were not feasible. Our appraisal of study quality and relevance of findings was based on established frameworks.[9 10] We focused on the available evidence from research studies and excluded other types of information. We extracted data on harmful effects in order to complement our review and found rates

of procedure failure and pneumonia that were higher than in previously published papers.[47 48] Eight of the 17 studies included children as the main study population or as a subgroup. In order to be comprehensive, we presented the available data on pre-hospital intubation in children while acknowledging that the care for very young TBI patients is specific and the trade-off between benefit and harm of intubation may be different for them.[49]

Clinical interpretation of findings

Given the relative uncertainty from the research, additional factors may be important in a specific clinical situation, including oxygen saturation before and after initial oxygen therapy, ventilation before and after manual clearing of the upper airway, facial trauma, and anticipated delays until definitive trauma care. A more conservative attitude towards pre-hospital intubation has been proposed in a current guideline[50] and, in particular, if expected transport time is short.[51] In addition, the availability of well-trained OHEMS teams with low intubation failure rates may be an argument for more permissive use of pre-hospital intubation. However, if this invasive procedure and the ensuing mechanical ventilation are performed poorly, the negative effects may outweigh potential benefits.[18] There were few reports of harm from intubation in the included studies. Multiple and prolonged intubation attempts, inadequate oxygenation, or excessive ventilation can contribute to secondary brain insult. Adequate training of staff is therefore crucial and should be the subject of future quality improvement studies. Both hyper- and hypocapnia may be strong components in secondary brain insult.[52] However, we emphasize that, although the effectiveness of pre-hospital intubation is uncertain, the situation may be different for other pre-hospital interventions. For instance, supplemental oxygen is recommended in recent guidelines.[10]

We found few studies planned explicitly to address our study question and no randomized trials. Well-designed randomized and non-randomized studies are needed to further elucidate whether, and in what circumstances, pre-hospital intubation is beneficial or harmful. Such studies could be strengthened by the following methodological features:

(i) recording of severity of TBI and concomitant injuries using standard classification schemes;
(ii) clear definition and description of control interventions;
(iii) intubation training of OHEMS staff (e.g. minimum of 60 intubations);[53]
(iv) definition of organizational characteristics of participating OHEMS and hospitals, as they influence patient outcome;[54 55]
(v) reporting of patient volume of participating trauma centres (larger centres were found to have lower mortality);[56]
(vi) adherence to accepted standard procedures for intubation and monitoring of harmful effects of intubation;
(vii) collection of data on respiratory and ventilation measures including hypocarbia during the pre-hospital period; blood gas analyses at the time of hospital admission;
(viii) documentation of delays between accident and clinical decision about neurosurgery (e.g. defined by the time of neurosurgical consultation);
(ix) the use of validated outcome measures (e.g. extended Glasgow outcome score) at fixed and meaningful time points[57] and blinding of those assessing outcomes to study interventions or important predictive factors;
(x) monitoring of loss to follow-up at all stages.

In conclusion, current evidence on the efficacy and harm of pre-hospital intubation in TBI patients comes mostly from observational studies, many of which are retrospective database studies. Overall, we found that the included studies were of low methodological quality, reported on few critical outcomes except for in-hospital mortality, and had inconsistent results. Consequently, we regarded the studies as insufficient to underpin any generally applicable recommendation for pre-hospital intubation. This underlines the general notion that the evidence base to define best practice for pre-hospital TBI care is insufficient.[58] The benefit and harm of pre-hospital intubation likely depend on additional factors including organization of emergency medical services, skills of staff, risk of procedure failure, and expected transport times. If such factors are well known in a given clinical situation, they should be used to inform the decision-making on the accident scene.

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