

Effect of Early Versus Late Tracheostomy or Prolonged Intubation in Critically Ill Patients with Acute Brain Injury: A Systematic Review and Meta-Analysis

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Abstract

Background The optimal timing of tracheostomy placement in acutely brain-injured patients, who generally require endotracheal intubation for airway protection rather than respiratory failure, remains uncertain. We systematically reviewed trials comparing early tracheostomy to late tracheostomy or prolonged intubation in these patients.

Methods We searched 5 databases (from inception to April 2015) to identify randomized controlled trials comparing early tracheostomy (≤ 10 days of intubation) with late tracheostomy (> 10 days) or prolonged intubation in acutely brain-injured patients. We contacted the principal authors of included trials to obtain subgroup data. Two reviewers extracted data and assessed risk of bias. Outcomes included

long-term mortality (primary), short-term mortality, duration of mechanical ventilation, complications, and liberation from ventilation without a tracheostomy. Meta-analyses used random-effects models.

Results Ten trials (503 patients) met selection criteria; overall study quality was moderate to good. Early tracheostomy reduced long-term mortality (risk ratio [RR] 0.57, 95 % confidence interval (CI), 0.36–0.90; $p = 0.02$; $n = 135$), although in a sensitivity analysis excluding one trial, with an unclear risk of bias, the significant finding was attenuated (RR 0.61, 95 % CI, 0.32–1.16; $p = 0.13$; $n = 95$). Early tracheostomy reduced duration of mechanical ventilation (mean difference [MD] -2.72 days, 95 % CI, -1.29 to -4.15 ; $p = 0.0002$; $n = 412$) and ICU length of stay (MD -2.55 days, 95 % CI, -0.50 to -4.59 ; $p = 0.01$; $n = 326$). However, early tracheostomy did not reduce short-term mortality (RR 1.25; 95 % CI, 0.68–2.30; $p = 0.47$; $n = 301$) and increased the probability of ever receiving a tracheostomy (RR 1.58, 95 % CI, 1.24–2.02; $0 < 0.001$; $n = 377$).

Prospero Our protocol was registered with PROSPERO (No: CRD42014010405).

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Conclusions Performing an early tracheostomy in acutely brain-injured patients may reduce long-term mortality, duration of mechanical ventilation, and ICU length of stay. However, waiting longer leads to fewer tracheostomy procedures and similar short-term mortality. Future research to explore the optimal timing of tracheostomy in this patient population should focus on patient-centered outcomes including patient comfort, functional outcomes, and long-term mortality.

Keywords Acute brain injury · Early tracheostomy · Tracheostomy timing · Prolonged endotracheal intubation · Mortality

Introduction

Most patients suffering from significant acute brain injury require airway protection and mechanical ventilation in the acute period, generally with an endotracheal tube. This translaryngeal approach, which makes oral care, communication, and feeding challenging, is usually poorly tolerated unless sedation is administered. Thus, clinicians often consider exchanging this tube for a tracheostomy. The anticipated benefits of tracheostomy include enhanced comfort, improved pulmonary hygiene, and decreased sedation requirements, all of which should accelerate liberation from the ventilator and discharge from critical care. However, this procedure is not without risks. Early complications include esophageal and airway injury, stomal bleeding, and barotrauma; and delayed complications include infections, tracheomalacia, tracheal stenosis, and tracheoinnominate fistula.

Observational studies conducted in acutely brain-injured patients suggest that early tracheostomy may be associated with lower in-hospital morbidity and improved clinical outcomes [1–5], but results are inconsistent and subject to confounding by indication. Systematic reviews of randomized controlled trials (RCTs) in mixed critical care populations have generally not found benefit from early tracheostomy (generally defined as occurring within 10 days of intubation) [6–8]. These results may not apply to acutely brain-injured patients, who typically require airway protection for depressed airway reflexes rather than respiratory failure. Consequently, early tracheostomy in brain-injured patients may expedite liberation from the ventilator while maintaining airway patency [9].

Our primary objective was to systematically review all RCTs and quasi-randomized controlled trials comparing early tracheostomy to late tracheostomy or prolonged intubation in acutely brain-injured patients to determine effects on long-term, all-cause mortality.

Methods

We conducted this systematic review using a predefined protocol according to current standards [10] and adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [11, 12]. The Research Ethics Board of Sunnybrook Health Sciences Centre reviewed the study and deemed it exempt from review. Our protocol was registered with PROSPERO: International prospective register of systematic reviews (No: CRD42014010405); available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014010405.

Search Strategy

We searched MEDLINE (1966–April 2015), EMBASE (1974–April 2015), CINAHL (1982–April 2015), CENTRAL (April 2015), and Web of Science (April 2015) (details in Supplemental Digital Content—Search Strategy) to identify RCTs and quasi-randomized trials comparing early tracheostomy with late tracheostomy or prolonged intubation. MEDLINE and EMBASE citations were limited to RCTs using sensitive strategies [13, 14]. To search gray literature, we hand-searched conference proceedings of the American Thoracic Society (1994–2015), Society of Critical Care Medicine (1994–2015), European Society of Intensive Care Medicine (1994–2015), American College of Chest Physicians (1994–2015), and the International Symposium on Intensive Care and Emergency Medicine (1999–2015). We contacted primary investigators of eligible abstracts for further information. Finally, we searched for unpublished and ongoing trials in <http://www.clinicaltrials.gov> and <http://www.controlled-trials.com>. No language restrictions were applied.

Trial Selection

Two reviewers (V.A.M., A.S.A.) independently screened studies for inclusion, retrieved potentially relevant studies, and decided on study eligibility. We selected RCTs and quasi-randomized trials comparing early tracheostomy (performed within 10 days of intubation) to late tracheostomy (performed after the 10th day of intubation) or prolonged intubation in intubated adults with acute brain injury (traumatic brain injury, aneurysmal subarachnoid hemorrhage, acute ischemic stroke, spontaneous intracerebral hemorrhage, postcraniotomy, global cerebral anoxia due to cardiac arrest, status epilepticus, meningitis, encephalitis, or cerebral abscess). Quasi-randomized trials included those allocating participants to treatment arms by

alternate or predictable assignment. We included studies that reported on all-cause mortality at any time.

Data Abstraction

Two reviewers (V.A.M., A.S.A.) independently abstracted data and methodological characteristics from the included trials using a standard form (Supplemental Digital Content). Disagreements were resolved by consensus and, if necessary, in consultation with a third reviewer (D.C.S.). We contacted investigators to obtain subgroup data for acutely brain-injured patients from trials conducted in the general critical care population (Supplemental Digital Content).

Risk of Bias

Two reviewers (V.A.M. and A.S.A.) independently assessed the risk of bias (selection, performance, detection, attrition, and reporting bias) for each included trial. Any disagreement was resolved through discussion with a third reviewer (D.C.S.). We used the Cochrane Collaboration's tool [15] to assess risk of bias at the study level according to the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting.

Outcomes

The primary outcome was long-term, all-cause mortality, defined as deaths reported at 6–12 months following acute brain injury. Secondary outcomes were short-term mortality, ICU mortality, hospital mortality, ICU length of stay, ventilator-associated pneumonia (VAP), duration of mechanical ventilation, duration of sedation, time to mobility, laryngotracheal complications (epiglottitis, vocal cords, larynx, or subglottic ulceration and inflammation, or tracheostomy complications), and liberation from mechanical ventilation without a tracheostomy. Short-term mortality was defined as in-hospital mortality or, if not available, at 60 days after randomization. Three trials did not specify the timing of mortality assessment and were only included in the short-term mortality analysis [9, 16, 17].

Subgroup and Sensitivity Analyses

A priori subgroup analyses were conducted to explore heterogeneity in the primary and secondary outcomes of long- and short-term mortality: (a) year of publication

(before vs. after median year); (b) size of trial (below vs. above median number of patients); (c) low risk versus non-low risk of bias; (d) timing of early tracheostomy (1–3 days vs. 4–10 days); (e) patient population (traumatic brain injury vs. mixed acute brain injuries); (f) control group (late tracheostomy vs. prolonged intubation only); and (g) type of tracheostomy (percutaneous vs. surgical). We also planned sensitivity analyses to explore the influence of analysis methods (per-protocol analysis vs. intention to treat), risk of bias, and exclusion of studies enrolling heterogeneous trauma patients on outcomes.

Quantitative Data Synthesis

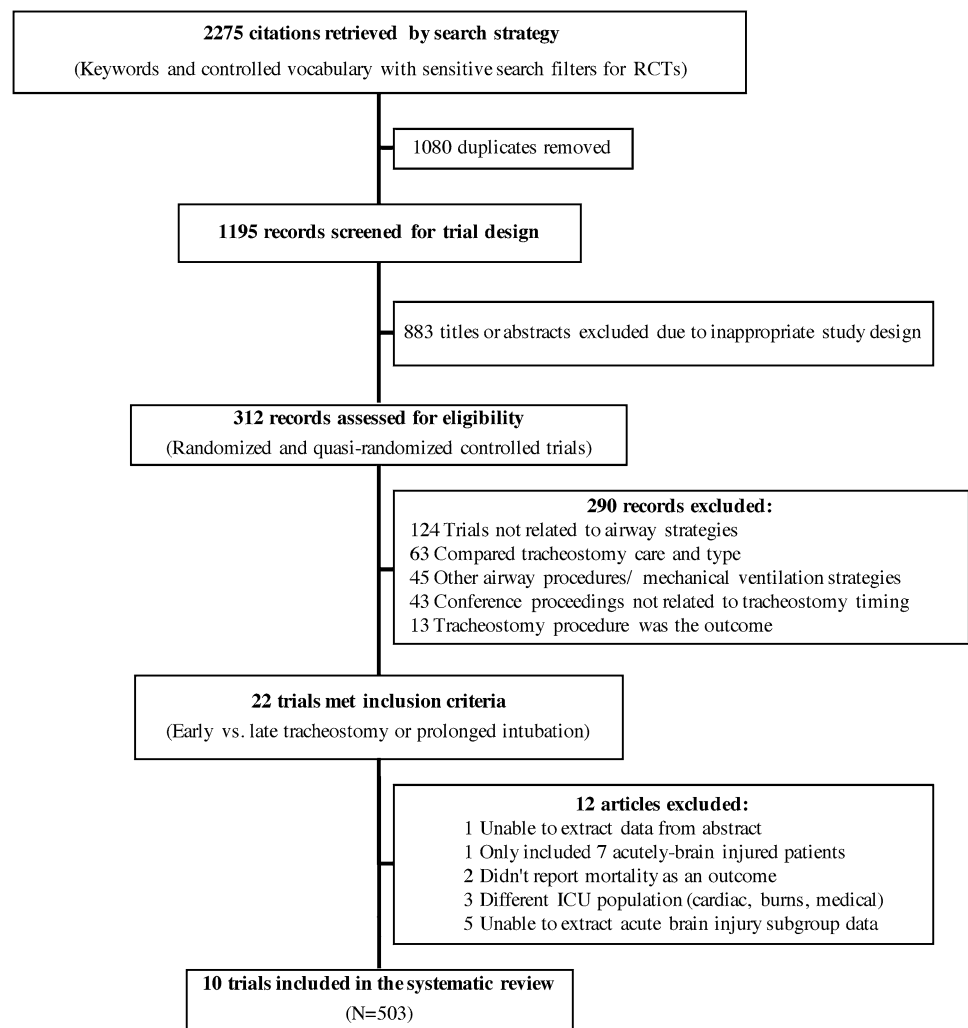
We used random effects models [18] to calculate pooled estimates of effect sizes using Review Manager 5.3.5 software (Cochrane Collaboration, Oxford, UK). Pooled continuous-effect measures were expressed as mean differences (MD) and pooled dichotomous effect measures as risk ratios (RR), both with 95 % confidence intervals (CI). We performed a z test of interaction for all subgroup comparisons, which tests the null hypothesis that the treatment effects in each subgroup are the same. Our analyses adhered to the intention-to-treat principle. Trials with zero deaths in either treatment arm were included by adding 0.5 to each cell [19]. We assessed between-study statistical heterogeneity for each outcome using the I^2 measure [20, 21], with suggested thresholds for low (25–49 %), moderate (50–74 %), and high (≥ 75 %) values of I^2 . We decided not to report meta-analyses in the presence of high statistical heterogeneity. To assess for publication bias, we examined a funnel plot of trial effect size versus trial precision [22].

Results

Literature Search

We identified 2275 citations from searches of electronic bibliographies and two citations from the gray literature. We retrieved 22 articles for detailed evaluation, 12 of which were excluded for the following reasons: inability to obtain acutely brain-injured subgroup data [23–26], incomplete data from published abstract [27], lack of acutely brain-injured patients (e.g. cardiac surgery, burns, and general medical patients) [28–31], and no mortality data [32–34] (Supplemental Digital Content—Tables 1 and 2). Ten trials enrolling 503 patients [9, 16, 17, 35–41] met the inclusion criteria for our review (Fig. 1; Table 1). The authors of 4 trials provided us with previously unpublished subgroup data for acutely brain-injured patients

Fig. 1 Study flow diagram in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement



[35, 36, 40, 41]. We also contacted several trial investigators to clarify study procedures [9, 16, 17, 37, 39]. Four trials found in trial registries were actively recruiting patients or recently terminated (Supplemental Digital Content—Table 3).

Study Characteristics and Methodological Quality

Table 1 summarizes the study characteristics of 10 included randomized controlled trials (see Supplemental Digital Content—Table 4 for patient characteristics). The majority of trials performed early tracheostomies within the first 5 days [17, 35, 38–41], while only one trial used a timeframe up to 10 days [37]. The control group was late tracheostomy in five trials [16, 35–38], prolonged translaryngeal intubation in three trials [9, 40, 41], and late tracheostomy or prolonged intubation in two trials [17, 39]. Six trials exclusively enrolled patients with traumatic brain injury [9, 16, 17, 36, 38, 41], three trials included patients with mixed causes of acute brain injury

[35, 37, 40], and one trial enrolled stroke patients only [39]. Studies used different definitions of VAP (Supplemental Digital Content—Table 5): Centers for Disease Control and Prevention (CDC) criteria [9, 16, 42], criteria closely aligned to CDC [17, 38], or American Thoracic Society consensus statement and guidelines [43, 44] for diagnosis of ICU-acquired pneumonia [40, 41]. Overall, the quality of the included trials was moderate to good (Supplemental Digital Content—Table 6 and Fig. 1). Visual inspection of the funnel plot for hospital mortality did not suggest publication bias.

Quantitative Data Synthesis

Primary Outcome

The primary outcome of long-term mortality was reported at 6 months [39, 41] and 1 year [35]; meta-analysis showed that early tracheostomy reduced long-term mortality (RR

Table 1 Summary of characteristics of included studies

| Study | Country | Centers | Study population/type of ICU | N (ABI) | Early tracheostomy ^a | Late tracheostomy ^a or prolonged intubation | Time of primary mortality endpoint ^b | Funding |
|---------------------------------|---------|---------|----------------------------------------------------------------------------|-----------------|---------------------------------|--------------------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| Dunham ^c 2014 [38] | USA | SC | Blunt, severe TBI | 31 | Day 3–5 (n = 17) ^d | LT Day 10–14 (n = 14) ^d | Hospital | NR |
| Mohamed 2014[37] | Egypt | MC | TBI, CVA | 24 ^e | Day 1–10 (n = 15) | LT > 10 days (n = 9) | Hospital | NR |
| Bösel 2013 [39] | Germany | SC | Severe stroke (nontraumatic ICH, SAH, AIS) | 60 | Days 1–3 (n = 30) ^f | LT/PI Days 7–14 (n = 30) ^f | ICU 6 months ^b | Provision of part of the tracheostomy kits by the manufacturer |
| Young ^g 2013 [35] | UK | MC | SDH, SE, ICH, meningitis, encephalitis, infected CSF shunt, encephalopathy | 35 | ≤4 days (n = 21) | LT ≥ 10 days (n = 14) | ICU | UK Intensive Care Society and the Medical Research Council |
| Fayed ^h 2012 [41] | Egypt | SC | Closed, severe TBI | 40 | Day 1 (n = 20) | PI (n = 20) | Hospital 1 year ^{b1} | NR |
| Terragni 2010 [36] | Italy | MC | TBI with ICP monitoring | 102 | After 6–8 days (n = 48) | LT After 13–15 days (n = 54) | 28 days | Regione Piemonte Ricerca Sanitaria Finalizzata |
| Blot 2008 [40] | France | MC | Neurological disease ^j | 22 | ≤4 days (n = 9) | PI ^k (n = 13) | 60 days | Association fédérative Nationale pour le Traitement à Domicile de l'Insuffisance Respiratoire Chronique |
| Barquist ^l 2006 [16] | USA | SC | TBI/polytrauma ^m | 60 | ≤7 days (n = 29) ⁿ | LT ≥ 29 days (n = 31) ⁿ | Presumed short-term | NR |
| Bouderka 2004 [19] | Morocco | SC | Severe TBI | 62 | Days 5–6 (n = 31) | PI (n = 31) | Presumed short-term | NR |

Table 1 continued

| Study | Country | Centers | Study population/type of ICU | N (ABI) | Early tracheostomy ^a | Late tracheostomy ^a or prolonged intubation | Time of primary mortality endpoint ^b | Funding |
|--------------------|---------|---------|------------------------------|-----------------|---------------------------------|--------------------------------------------------------|-------------------------------------------------|---------|
| Sugarman 1997 [17] | USA | MC | Severe TBI | 67 ^o | Days 3–5 (n = 35) | LT/PI ≥10–14 days (n = 32) | Presumed short-term | NR |

^a Day of tracheostomy after translaryngeal intubation

^b Primary mortality endpoint was not specified in the trial

^{b1} Primary mortality endpoint for the trial was all-cause mortality at 30 days. This data was not provided in the subgroup data supplied by the authors

^c Due to a slow accrual rate of appropriate patients, the study was terminated early

^d Authors state that for a few patients where families voiced a strong opinion, early tracheostomy or no early tracheostomy was according to their request, regardless of randomization allocation

^e Authors included 3 cervical spine injury patients in the TBI group who received a late tracheostomy, we excluded these patients from our review

^f 1 patient did not receive an early tracheostomy and crossed over to late tracheostomy. Median time to tracheostomy in the late group 10.5 days (IQR 9-11)

^g After an independent Data Monitoring and Ethics Committee reviewed unblinded data from an interim analysis using a Haybittle-Peto boundary rule (the study would continue unless the primary outcome was different between the groups at $P < 0.001$ at interim analysis), the trial was terminated early due to study fatigue indicated by a decreasing average per center recruitment rate. The a priori planned sample size was not achieved; the final sample of 899 patients available for analysis of the primary outcome had the power to detect an 8.3 % absolute change in 30-day mortality from the “late” group value of 31.5 % with 80 % power

^h Data extracted from the published abstract and provisional unpublished manuscript supplied by the corresponding author. Data was taken from Group II (20 patients to where percutaneous endoscopic gastrostomy was placed within 24 h and patients remained intubated via translaryngeal route) and Group III (20 patients where tracheostomy and percutaneous endoscopic gastrostomy were placed within 24 h of endotracheal intubation)

ⁱ Mortality was recorded for patients after the first 3 weeks until hospital discharge or death, whichever came first, for a maximum of 6 months

^j Patients with “main underlying pathology” coded “neurological” were included; the study database did not record if this underlying neurological pathology was acute or not (personal communication with study authors). Patients were excluded if they had an irreversible neurological disease or post-trauma intracranial hypertension (intracranial pressure > 20 cmH₂O and/or cerebral edema on head CT scan)

^k Patients in control group could not receive tracheostomy until at least 14 days after translaryngeal intubation, 3 ultimately received a tracheostomy

^l The study was halted after the first interim analysis as no significant difference was found between groups in any of the outcome parameters

^m Patients were eligible for enrollment if GCS > 4 with a negative brain CT (no anatomic head injury), or a GCS > 9 with a positive head CT (known anatomic head injury)

ⁿ 2 patients, 1 from early and 1 from late group, were intubated on their 3rd day of admission. This was an ITT study, 27 out of 29 of the patients in the early group and 11 out of 31 in the late group had a surgical tracheostomy placed. 5 patients in the early group had their tracheostomy placed delayed by an average of 3 days because of ARDS requiring high levels of positive end expiratory pressure. 4 patients in the late group had a surgical tracheostomy placed on days 17, 18, 19, and 21 to facilitate transfer to long-term care

^o 3 separate randomized groups in this study: primary head trauma (GCS ≤ 8), non-head trauma (GCS ≤ 8), critically ill nontrauma respiratory failure. Only patients with primary head trauma were included

^N number of patients; *ABI* acute brain injury; *ARDS* acute respiratory distress syndrome; *LT* late tracheostomy; *PI* prolonged intubation; *MC* multicenter; *SC* single center; *TBI* traumatic brain injury; *CVA* cerebral vascular accident; *ICH* intracerebral hemorrhage; *SAH* subarachnoid hemorrhage; *AIS* acute ischemic stroke; *SDH* subdural hemorrhage; *SE* status epilepticus; *CSF* cerebrospinal fluid; *ICP* intracranial pressure; *NR* not reported; *GCS* Glasgow Coma Scale; *CT* computerized tomography; *ITT* intention-to-treat

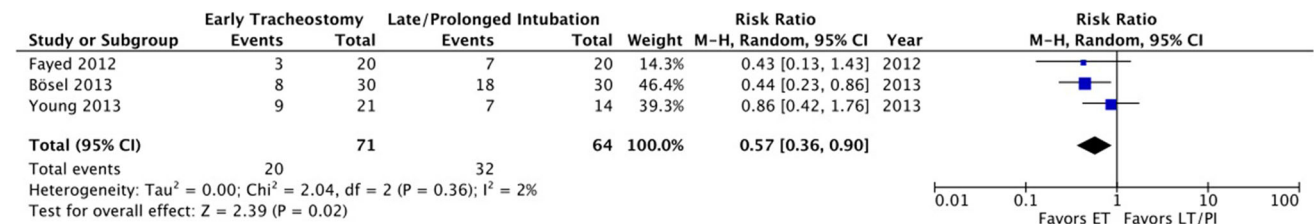


Fig. 2 Long-term mortality: Random-effects meta-analysis of early tracheostomy versus late tracheostomy or prolonged intubation on long-term mortality, expressed as the risk ratio (RR), with values more than 1 indicating increased mortality with early tracheostomy. Each *black square* and *horizontal line* denotes the point estimate and 95 % CI for each trial’s RR. The *diamond* signifies the pooled RR for all trials, with the *center* denoting the point estimate and the width the 95 % CI. Weight is the contribution of each study to the overall RR.

Young et al. measured mortality at 1 year, Bösel et al. measured at 6 months, Fayed et al. recorded mortality until hospital discharge or death (whichever came first) for a maximum of 6 months. *ET* early tracheostomy group, *LT/PI* late tracheostomy or prolonged intubation, *I²* percentage of total variation across studies from between-study heterogeneity rather than chance, *CI* confidence interval

Table 2 Summary of meta-analysis results

| Outcomes | Number of studies | Number of patients providing data | Effect Estimate [^] [95 % CI] | P value for effect estimate | I ² (%) |
|-----------------------------------------------------------|-------------------|-----------------------------------|----------------------------------------|-----------------------------|--------------------|
| Primary outcome | | | | | |
| Long-term mortality* [35, 39, 41] | 3 | 135 | RR 0.57 [95 % CI 0.36, 0.90] | 0.02 | 2 |
| Secondary outcomes:dichotomous outcomes | | | | | |
| Short-term mortality [9, 16, 17, 35, 37, 38, 40] | 7 | 301 | RR 1.25 [95 % CI 0.68, 2.30] | 0.47 | 31 |
| Hospital mortality [#] [35, 37, 38, 40] | 4 | 112 | RR 1.17 [95 % CI 0.46, 2.94] | 0.74 | 38 |
| ICU mortality ⁺ [35, 36, 39] | 3 | 197 | RR 0.46 [95 % CI 0.24, 0.89] | 0.02 | 21 |
| Ventilator-associated pneumonia [9, 16, 17, 38, 40, 41] | 6 | 275 | RR 0.89 [95 % CI 0.65, 1.21] | 0.46 | 54 |
| Tracheostomy performed [16, 17, 35, 36, 38–40] | 7 | 277 | RR 1.58 [95 % CI 1.24, 2.02] | <0.001 | 70 |
| Laryngotracheal complications [9, 16, 39] | 4 | 122 | RR 2.54 [95 % CI 0.46, 13.88] | 0.28 | 59 |
| Continuous outcomes | | | | | |
| Duration of mechanical ventilation [9, 17, 35, 36, 38–41] | 8 | 412 | MD -2.72 [95 % CI -4.15, -1.29] | 0.0002 | 0 |
| Length of ICU stay [17, 35, 36, 39, 40] | 6 | 326 | MD -2.55 [95 % CI -4.59, -0.50] | 0.01 | 0 |

* Three studies with longer-term follow-up; Bösel and Fayed measured mortality at 6 months and Young at 1 year

Hospital mortality was a composite of hospital or 60-day mortality

+ ICU mortality was a composite of ICU and 28-day mortality

[^] Pooled risk ratio or mean difference calculated using a random-effects model [95 % confidence interval]. Direction of effect estimate: RR <1.0 favors early tracheostomy, RR >1.0 favors late tracheostomy or prolonged intubation; MD <0 favors early tracheostomy, MD >0 favors late tracheostomy or prolonged intubation

RR risk ratio; CI confidence interval; MD mean difference. All analyses used random-effects models

0.57, 95 % CI, 0.36–0.90; *p* = 0.02; three trials; *n* = 135; 52 events; I² 2 %; Fig. 2, Table 2, Supplemental Digital Content—Table 7). In a sensitivity analysis excluding one trial [41] with an unclear risk of bias, the significant finding was attenuated (RR 0.61, 95 % CI, 0.32–1.16; *p* = 0.13; *n* = 95; two trials; I² 43 %). There were insufficient trials to perform other subgroup and sensitivity analyses.

Secondary Outcomes

Short-Term Mortality

Seven trials (301 participants) provided data for all-cause, short-term mortality [9, 16, 17, 35, 37, 38, 40] that was reported at hospital discharge [35, 37, 38], 60 days [40], or

Table 3 Subgroup and sensitivity analysis of short-term mortality

| Outcomes | Number of studies | Number of patients providing data | Effect estimate* [95 % CI] | P value for effect estimate | I ² ** (%) |
|----------------------------------------------------------------------------------------------------------------|-------------------|-----------------------------------|----------------------------|-----------------------------|-----------------------|
| Short-term mortality by median number of patients | | | | | |
| ≥35 patients [9, 16, 17, 35] | 4 | 124 | 1.23 [0.61, 2.47] | 0.56 | 30 |
| <35 patients [37, 38, 40] | 3 | 77 | 1.57 [0.22, 11.30] | 0.65 | 59 |
| The z test for subgroup interaction was not statistically significant ($p = 0.82$) | | | | | |
| Short-term mortality by median year of publication [^] | | | | | |
| 2008–2015 [35, 37, 38, 40] | 4 | 112 | 1.17 [0.46, 2.94] | 0.74 | 38 |
| Before 2008 [9, 16, 17] | 3 | 189 | 1.39 [0.47, 4.14] | 0.55 | 46 |
| The z test for subgroup interaction was not statistically significant ($p = 0.81$) | | | | | |
| Short-term mortality by risk of bias | | | | | |
| Low risk [35, 40] | 2 | 57 | NA** | NA** | 77 |
| Non-low risk [9, 16, 17, 37, 38] | 5 | 244 | 1.21 [0.64, 2.28] | 0.56 | 19 |
| The z test for subgroup interaction was not statistically significant (NA) | | | | | |
| Short-term mortality by different control arms | | | | | |
| Late tracheostomy [16, 35, 37, 38] | 4 | 150 | 0.84 [0.47, 1.51] | 0.56 | 0 |
| Prolonged intubation [9, 40] | 2 | 84 | 3.54 [0.41, 30.39] | 0.25 | 60 |
| The z test for subgroup interaction was not statistically significant ($p = 0.21$) | | | | | |
| Short-term mortality by etiology of brain injury | | | | | |
| Traumatic brain injury only [9, 16, 17, 38] | 4 | 140 | 1.20 [0.44, 3.30] | 0.72 | 37 |
| Mixed brain injury [35, 37, 40] | 3 | 81 | 1.37 [0.48, 3.96] | 0.56 | 54 |
| The z test for subgroup interaction was not statistically significant ($p = 0.86$) | | | | | |
| Sensitivity analyses | | | | | |
| Base case [9, 16, 17, 35, 37, 38, 40] | 7 | 301 | 1.25 [0.68, 2.30] | 0.47 | 31 |
| Per-protocol analysis [#] [9, 16, 17, 35, 37, 38, 40] | 7 | 288 | 1.11 [0.55, 2.24] | 0.76 | 52 |
| Intention-to-treat (patients lost to follow-up assumed to have died) ^{##} [9, 16, 17, 35, 37, 38, 40] | 7 | 301 | 0.98 [0.49, 1.97] | 0.95 | 63 |
| Base case with exclusion of mixed trauma trial ^{###} [9, 17, 35, 37, 38, 40] | 6 | 241 | 1.43 [0.77, 2.67] | 0.26 | 29 |

* Pooled risk ratio calculated using a random-effects model [95 % confidence interval]. Direction of effect estimate: RR <1.0 favors early tracheostomy, RR >1.0 favors late tracheostomy or prolonged intubation

** A meta-analysis was conducted only in case of low or moderate ($I^2 < 75 %$) statistical heterogeneity [20, 21]

[^] Recent studies may better reflect modern clinical practice

[#] Using a per-protocol analysis for two of the trials, rather than intention to treat [37, 38]

^{##} Using intention-to-treat analysis counting patients lost to follow-up as expired [37, 38]

^{###} Exclusion of one trial that excluded severe TBI, included patients with GCS >4 with negative brain CT or GCS >9 with positive head CT [16]

I^2 percentage of total variation across studies from between-study heterogeneity rather than chance; CI confidence interval; NA non-applicable

presumed short-term mortality [9, 16, 17], in keeping with previous systematic reviews [8, 45]. Short-term mortality was similar between groups (RR 1.25, 95 % CI, 0.68–2.30; $p = 0.47$; seven trials; $n = 301$; 61 events; Table 2, Supplemental Digital Content - Fig. 2). Additional analyses (Table 3) showed similar effects in all subgroups examined; sensitivity analyses using per-protocol analysis for two trials [37, 38], intention-to-treat analysis assuming that all patients lost to follow-up died [37, 38], or removing one trial that enrolled general trauma patients [16] did not change the treatment effect (Table 3).

Hospital and ICU Mortality

Four trials (112 patients; 29 events) recorded mortality at hospital discharge [35, 37, 38] or 60 days [40] and found similar hospital mortality in both arms (RR 1.17, 95 % CI, 0.46, 2.94; $p = 0.18$; I^2 38 %; Supplemental Digital Content—Fig. 3). Three trials (197 patients; 49 events) recorded mortality at ICU discharge [35, 39] or 28 days [36] and found lower ICU mortality with early tracheostomy (RR 0.46, 95 % CI, 0.24, 0.89; $p = 0.02$; I^2 21 %; Supplemental Digital Content—Fig. 4).

Rate of Tracheostomies and Laryngotracheal Complications

Seven trials (377 patients; 277 tracheostomies) reported the number of patients undergoing tracheostomy procedures in both groups [16, 17, 35, 36, 38–40]. As expected, patients in the early tracheostomy group were more likely to undergo the procedure (RR, 1.58, 95 % CI, 1.24, 2.02; $p < 0.001$; $n = 377$; seven trials; I^2 70 %; Supplemental Digital Content—Fig. 5). Pooled data from four studies (222 patients; 37 patients with complications) found no significant difference in laryngotracheal complications (RR 2.54, 95 % CI, 0.46–13.88; $p = 0.28$; I^2 59 %; Supplemental Digital Content—Fig. 6) [9, 16, 39, 41].

Other Secondary Outcomes

Early tracheostomy reduced the mean duration of ventilation by 2.72 days (95 % CI, -1.29 to -4.15 ; $p = 0.0002$; $I^2 = 0$ %; Supplemental Digital Content—Fig. 7) and the mean ICU length of stay by 2.55 days (95 % CI, -0.50 to -4.59 ; $p = 0.01$; $I^2 = 0$ %; Supplemental Digital Content—Fig. 8). There was no effect on VAP (RR 0.89, 95 % CI, 0.65–1.21; $p = 0.46$; I^2 54 %; Supplemental Digital Content—Fig. 9). Data on duration of sedation, length of hospital stay, and time to mobility were infrequently or nonuniformly reported, precluding meta-analysis. Furthermore, subgroup analyses regarding timing of early tracheostomy and type of tracheostomy could not be completed due to insufficient data.

Heterogeneity

Clinical heterogeneity among studies existed due to the inclusion of different brain injury etiologies, variable timing of early tracheostomy and mortality assessments, and variable risk of bias. However, all included studies were judged to be sufficiently similar to be pooled in meta-analyses. Statistical heterogeneity was low to moderate for all meta-analyses.

Discussion

Summary of Main Results

Our main finding of this systematic review is that early tracheostomy, compared with late tracheostomy or prolonged translaryngeal intubation, might lower ICU and long-term mortality. However, inferences are severely limited by the small number of studies and outcome events, and lack of consistency with the effect on mortality measured at hospital discharge or at other time points.

Therefore, the potential to improve survival with early tracheostomy should be seen as hypothesis-generating. A strategy of early tracheostomy also reliably increases the proportion of patients undergoing the procedure and reduces duration of mechanical ventilation and ICU length of stay; the latter two outcomes may be of more interest to health systems and/or payers than to patients [46]. Considering the procedural risks, acutely brain-injured patients with uncertain or poor neurological prognosis may be better served by waiting longer before committing to the options of tracheostomy or primary extubation [47, 48].

Most of the pooled outcome data from previous systematic reviews in the general critical care population do not show a significant reduction in mortality with early tracheostomy, compared to late tracheostomy or prolonged intubation [7, 8, 49, 50]. However, two recent meta-analyses, including an updated review pooling results using the largest number of patients to date, did show significantly lower long-term mortality with early tracheostomy [6, 51]. We similarly found that performing an early tracheostomy in acutely brain-injured patients within the first 10 days of intubation might reduce long-term mortality and may also lower ICU mortality.

We also found that early tracheostomy significantly reduced the durations of mechanical ventilation and stay in the ICU, which may facilitate an earlier discharge to a non-ICU setting or transfer to a long-term acute care facility (LTACF) [52, 53]. A recent study found a steep rise over the past 20 years in rates of discharge to LTACFs after tracheostomy, from 40 % in 1993 to 72 % in 2012 [54]. Performing an early tracheostomy in acutely brain-injured patients may simply be shifting the location of deaths to these LTACFs, where overall mortality has been shown to be high [55]. However, this shift in discharge location may benefit the healthcare system by improving access to acute hospital resources, enabling discharge to a lower-intensity care setting at an earlier point in the admission period [46].

Strengths and Limitations

This review followed a predetermined protocol [56] for methodology and statistical analysis. Our extensive search strategy and inclusion of additional data from primary study authors allowed us to complete this novel synthesis of data for the role of early tracheostomy in brain-injured patients [6, 8, 49]. We incorporated unpublished literature, noting that such trials are of similar methodological quality compared to published trials [57] and did not find evidence of publication bias among the included trials.

Nevertheless, our study has a number of important limitations. First, the data are relatively sparse, and we were unable to incorporate data from four trials. Larger future trials are likely to modify the pooled analyses and conclusions. Secondly, studies were heterogeneous and

included single and multicenter trials, percutaneous and surgical techniques, different timings of early tracheostomy (all within 10 days of intubation), and mixed acutely brain-injured populations. However, we did not identify any subgroup effects; and results were consistent in several a priori sensitivity analyses [10]. We were unable to explore in any depth subgroups of acutely brain-injured patients and cannot determine whether further trials should enroll homogenous patient groups by etiology, pathophysiological mechanisms or anatomic types [58], which may be relevant considerations for airway protection and ventilation failure.

Given our results, along with two recently terminated and unreported trials of early tracheostomy in severe brain injury [59, 60], physicians at the bedside lack definitive guidance regarding tracheostomy timing in brain-injured patients. Results from the ongoing SETPOINT 2 trial (ClinicalTrials.gov identifier: NCT02377167) may help to further define the role of early tracheostomy in at least one subgroup of severe stroke patients. In the meantime, clinical decisions for acutely brain-injured patients should be informed by existing RCTs or rigorously conducted meta-analyses of these RCTs [61, 62].

Conclusions

This systematic review suggests that performing an early tracheostomy in acutely brain-injured patients within the first 10 days of intubation may reduce long-term and ICU mortality while significantly reducing duration of mechanical ventilation and ICU stay. However, limited numbers of randomized patients and outcome events place serious limitations on the strength of these conclusions. Future trials of optimal timing of tracheostomy in this patient population should focus on patient-centered outcomes including comfort, mobility, functional outcomes, longer-term mortality, and discharge destination from the hospital.

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Authors' Contributions V.A.M. contributed to the literature search, study design, data analysis, data interpretation, writing, critical revision, and final approval. A.A.A. contributed to the study design, data interpretation, critical revision, and final approval.

N.K.J.A. contributed to the study design, data interpretation, critical revision, and final approval. D.C.S. contributed to data interpretation, critical revision, and final approval. G.D.R. contributed to the study design, data interpretation, critical revision, and final approval. B.H.C. contributed to the study design, data interpretation, critical revision, and final approval. A.B.N. contributed to the study design, data analysis, data interpretation, writing, critical revision, and final approval.

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Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to declare.

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