Tracheal intubation in traumatic brain injury
a multicentre prospective observational study
Gravesteijn, Benjamin Yael; Sewalt, Charlie Aletta; Nieboer, Daan; Menon, David Krishna; Maas, Andrew; Lecky, Fiona; Klimek, Markus; Lingsma, Hester Floor; CENTER-TBI collaborators
Published in:
British Journal of Anaesthesia
DOI:
10.1016/j.bja.2020.05.067
Publication date:
2020
Document version
Final published version
Document license
CC BY
Citation for published version (APA):
Gravesteijn, B. Y., Sewalt, C. A., Nieboer, D., Menon, D. K., Maas, A., Lecky, F., Klimek, M., Lingsma, H. F., & CENTER-TBI collaborators (2020). Tracheal intubation in traumatic brain injury: a multicentre prospective observational study. British Journal of Anaesthesia, 125(4), 505-517. https://doi.org/10.1016/j.bja.2020.05.067
Terms of use
This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:
• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying this open access version
If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk
Tracheal intubation in traumatic brain injury: a multicentre prospective observational study

Benjamin Yael Gravesteijn1,2,*, Charlie Aletta Sewalt2, Daan Nieboer2, David Krishna Menon3, Andrew Maas4, Fiona Lecky5, Markus Klimek1, Hester Floor Lingsma2, on behalf of the CENTER-TBI collaborators

1Department of Anaesthesiology, Erasmus University Medical Centre, Rotterdam, the Netherlands, 2Department of Public Health, Erasmus University Medical Centre, Rotterdam, the Netherlands, 3Department of Anaesthesiology, University of Cambridge, UK, 4Department of Neurosurgery, University Hospital Antwerp, Antwerp, Belgium and 5Emergency Medicine Research in Sheffield (EMRiS), School of Health and Related Research (ScHARR), Faculty of Medicine, Dentistry and Health, University of Sheffield, Sheffield, UK

*Corresponding author. E-mail: b.gravesteijn@erasmusmc.nl

The members of the CENTER-TBI collaborators are listed at the Acknowledgments section.

Abstract

Background: We aimed to study the associations between pre- and in-hospital tracheal intubation and outcomes in traumatic brain injury (TBI), and whether the association varied according to injury severity.

Methods: Data from the international prospective pan-European cohort study, Collaborative European NeuroTrauma Effectiveness Research for TBI (CENTER-TBI), were used (n=4509). For prehospital intubation, we excluded self-presentation. For in-hospital intubation, patients whose tracheas were intubated on-scene were excluded. The association between intubation and outcome was analysed with ordinal regression with adjustment for the International Mission for Prognosis and Analysis of Clinical Trials in TBI variables and extracranial injury. We assessed whether the effect of intubation varied by injury severity by testing the added value of an interaction term with likelihood ratio tests.

Results: In the prehospital analysis, 890/3736 (24%) patients had their tracheas intubated at scene. In the in-hospital analysis, 460/2930 (16%) patients had their tracheas intubated in the emergency department. There was no adjusted overall effect on functional outcome of prehospital intubation (odds ratio=1.01; 95% confidence interval, 0.79–1.28; P=0.96), and the adjusted overall effect of in-hospital intubation was not significant (odds ratio=0.86; 95% confidence interval, 0.65–1.13; P=0.28). However, prehospital intubation was associated with better functional outcome in patients with higher thorax and abdominal Abbreviated Injury Scale scores (P=0.009 and P=0.02, respectively), whereas in-hospital intubation was associated with better outcome in patients with lower Glasgow Coma Scale scores (P=0.01): in-hospital intubation was associated with better functional outcome in patients with Glasgow Coma Scale scores of 10 or lower.

Conclusion: The benefits and harms of tracheal intubation should be carefully evaluated in patients with TBI to optimise benefit. This study suggests that extracranial injury should influence the decision in the prehospital setting, and level of consciousness in the in-hospital setting.

Clinical trial registration: NCT02210221.

Keywords: effectiveness; Europe; neurological outcome; prehospital; tracheal intubation; traumatic brain injury
Editor’s key points

- It is difficult to know whether to intubate and institute mechanical ventilatory support for those with traumatic brain injuries.
- This large observational study suggests that the indications for tracheal intubation in the setting of traumatic brain injury should be the extent of extracranial injury and the severity of brain injury.
- Patients with extensive extracranial injury might benefit from intubation before arrival at the hospital.
- Those with impaired level of consciousness as assessed by the Glasgow Coma Scale might benefit from tracheal intubation shortly after they arrive at the hospital.

The burden of traumatic brain injury (TBI) is high: it is a leading cause of injury-related death and disability.1 TBI is estimated to be responsible for 287.2 hospital admissions and 11.7 deaths per 100 000 persons per year in Europe.2 Mortality rates are higher for moderate and severe TBIs compared with mild TBIs. Although the primary injury arising at the time of impact cannot be mitigated, secondary brain injury arising from subsequent hypoxaemia and hypotension worsens outcome and should be prevented.3–5

Hypoxaemia and hypotension are both influenced by intubation; tracheal intubation in patients who are not deeply comatose requires induction of anaesthesia and neuromuscular block.6,7 However, injudicious use of anaesthetics and positive pressure ventilation can cause hypotension, particularly in hypovolaemic trauma patients.8 Meanwhile, inadequate depth of anaesthesia during laryngoscopy may precipitate hypertension and (further) increase of intracranial pressure (ICP).9 Drug-assisted intubation can be technically challenging in patients with TBI, particularly under prehospital conditions. Under these conditions, positioning and lighting may be suboptimal. If there is also associated facial injury present, the risks of a ‘can’t intubate can’t ventilate’ scenario, or oesophageal intubation, are not negligible. Failure to rapidly control the airway owing to delayed or unsuccessful intubation attempts may lead to, or worsen, hypoxia or hypercapnia. These secondary insults are associated with worse outcomes for TBI patients, and may be mitigated or contributed to by decisions to intubate.10–13

The international guidelines of the Brain Trauma Foundation on intubation in TBI14 recommend intubation for patients with more severe injuries. However, the body of evidence underlying this recommendation consists of only class III evidence, mostly from small retrospective studies. The exception is a randomised trial by Bernard and colleagues15 showing benefit of prehospital vs in-hospital intubation in injured prehospital patients with a Glasgow Coma Scale (GCS) score <9. These data have driven recommendations and practice: more severely injured patients, typically with a GCS score of 8 or lower, are intubated more often.16 However, the primarily observational associations that underpin this practice recommendation are prone to ‘confounding by indication’ bias.

Possibly partly as a result of the low quality of evidence, guideline adherence varies.17 For prehospital intubation (PHI), the estimate lies about 80% adherence, but a large range of 44%–92% adherence is observed in the literature.18,19 There is a need for prospective evidence, sufficiently adjusting for confounding bias.

The aim of this prospective study was to improve evidence supporting the guideline recommendations regarding PHI and in-hospital intubation (IHI). Given the practice variation in intubation, we wanted to assess the effect of intubation both at the patient level and at the trauma system level. In addition, given the guideline recommendations to intubate more severely injured patients, we explored whether GCS score and extracranial injury influence the effect of intubation on functional outcome. Finally, we wanted to replicate the RCT by Bernard and colleagues15 in the European setting, by comparing outcome of PHI vs intubation at the emergency department (ED) in patients whose tracheas were intubated.

Methods

This study was reported according to STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) guidelines.20

Study population

We studied patients who were included in the European, prospective, longitudinal cohort study, Collaborative European NeuroTrauma Effectiveness Research for Traumatic Brain Injury (CENTER-TBI). In this study, data from 4509 all-severity TBI patients in 59 centres throughout Europe had been collected in the period of 2014–2018 and were available for analysis. Further details of the CENTER-TBI study, including rationale for sample size, have been published elsewhere.21,22 A predetermined analysis plan was approved by the management committee before the actual analysis started.

Patient selection

We excluded patients in whom intubation could not have been considered. For PHI, we therefore excluded patients who arrived to the study hospital without activating emergency medical services (self-presenters). For the IHI analysis, we excluded patients whose tracheas were already intubated on scene.

Definitions

PHI was defined as intubation at the scene of injury. IHI was defined as intubation at the ED of the study hospital, or intubation at the referring hospital if the patient was transferred. Intubation could include intubation with and without sedation. The best prehospital GCS score was used for the analysis of PHI and for the analysis of PHI vs IHI. The GCS score at ED arrival was used for the analysis of IHI. The baseline GCS score was defined as the last GCS score in the ED (after stabilisation). If this was missing, or when the patient was sedated or when the patient’s trachea was intubated, a previous measurement moment was used: at ED arrival or prehospital, respectively. Outcome was measured using the Glasgow Outcome Scale – Extended (GOS-E) at 6 months after injury, GOS-E is an eight-point scale that measures functional outcome after TBI.23

For risk adjustment, we used variables from the IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI) model24 including age, GCS score, pupil...
reactivity, imaging characteristics (traumatic subarachnoid haemorrhage, epidural haematoma, Marshall CT class), physiological parameters at ED arrival (heart rate, systolic blood pressure, oxygen saturation), and also secondary insults during the ER treatment (hypoxia or hypotension at the ED). Hypoxia was defined as a documented \( P_{aO2} \) below 8 kPa (60 mm Hg), a documented \( S_{aO2} \) below 90%, or both, or in case of clinical suspicion (e.g. cyanosis, apnoea, or respiratory distress) when not documented. Hypotension was defined as a documented systolic blood pressure below 90 mm Hg, or in case of clinical suspicion (e.g. shock or absent brachial pulse) when not documented. Moreover, because extracranial injury is also described as a confounder,25 we also included abbreviated injury severity (AIS) scores of head, spine/chest, abdominal (including pelvis), limbs, and face. Finally, as literature suggests differences in outcome between men and women,26 we assumed sex to be a potential confounder as well.

**Statistical analysis**

For the patient-level descriptive analysis, baseline characteristics were compared between the PHI, IHI, and not-intubated (NI) group. Medians and inter-quartile ranges (IQRs) are reported for non-normally distributed variables; for normally distributed variables, means and standard deviations are reported.

Missing data were multiply imputed for the main analyses using the ‘mice’ package.27 The missing pattern was assumed to be missing at random. Together with the potential confounders and intubation, GOS-E was included in the imputation model. Five imputed datasets were obtained.

To assess the effect of intubation on outcome, proportional odds logistic regression was performed using intubation as independent variable and GOS-E as dependent variable, with adjustment for confounders. We allowed for non-linear effects by using restricted cubic splines with three degrees of freedom for heart rate, systolic blood pressure, saturation, and age, and with second-degree polynomials for AIS scores. Finally, to assess whether GCS score, abdominal AIS, or thorax AIS influenced the effect of intubation, interaction terms between these characteristics and intubation were added in a consecutive model. We present the effect of intubation as odds ratios (ORs) for more unfavourable outcome and 95% confidence intervals (CIs). The exception is the presentation of the interaction effect: because the interaction effect is based on the combination of two coefficients (the main effect of intubation and the interaction with injury severity), the interpretation is more complex. Instead, we only present the \( P \)-value of the overall test (likelihood ratio test) for interaction.

To investigate the relationship between intubation practice and outcome at the hospital level, we calculated the adjusted probabilities of intubation based on a multinomial mixed effects regression model. The covariates included in the model were based on previous work,28 and include age, GCS score, anatomical injury scales (head/neck thorax/chest, face, and abdomen), and pupil reactivity. A random intercept for centre, conditional on country, was used to adjust for random variation. Because we used multinomial regression, separate random intercepts for each centre were estimated for both outcomes (PHI and IHI). To define the outcome per centre, we calculated mean GOS-E scores per centre. The association between intubation preference and outcome was estimated with linear regression with the random intercepts per centre for IHI and PHI, and IHI or PHI itself as an independent variable and mean GOS-E per centre as a dependent variable. An interaction term between the intubation preference and PHI or IHI was included. The coefficient of the model was divided by 10 to calculate the coefficient per 10% increase in adjusted intubation rate. The coefficient for interaction between preference and intubation was added to the main effect. Only centres with more than 20 included patients were included in this analysis.

*Fig 1. Flowchart showing the number of patients excluded with each criterion. IHI, in-hospital intubation; PHI, prehospital intubation.*
Results

The CENTER-TBI database consists of 4509 patients, included across 59 centres in Europe. Information about intubation was present in a total of 3822 (85%) patients, who came from all participating centres (Fig. 1).

Prehospital intubation

In the PHI analysis, after excluding patients who self-presented at the ED (n=86), 3736 patients were included. Of these patients, 890 (24%) underwent tracheal intubation on scene. Of 3166 (85%) patients, a GOS-E was obtained at 6 months follow-up.

In this PHI subset, 571 (72.4%) of the patients with a prehospital GCS score of 8 or lower had their tracheas intubated on scene, and 212 (12%) of the patients with a prehospital GCS score higher than 8 had their tracheas intubated on scene (Fig. 2). On average, patients that had their tracheas intubated had lower baseline GCS score, were younger, and more often male. Furthermore, based on a threshold AIS > 3, patients who were intubated had a higher proportion of head and cervical spine injury, major chest/spine injury, and abdominal injury. In addition, patients whose tracheas were intubated had more intracranial pathologies, and suffered from more secondary hypoxic and hypotensive insults in the ED (Table 1). These differences were smaller when patients with GCS scores above 8 were excluded (Supplementary Table S1).

The hospital stay of patients that required PHI was characterised by a longer total length of stay, and a longer ICU stay, and more days of mechanical ventilation and sedation. In addition, pneumonia was observed more often in these patients, and more extracranial and intracranial surgeries, including decompressive craniectomies. Although the absolute ICP values in patients in whom it was measured did not differ substantially on average, the therapy intensity that they received was higher in patients who required intubation. Finally, the blood glucose concentrations were higher in patients who required intubation, both at day 1 as during the entire stay.

Before adjusting for possible confounders, PHI was associated with worse functional outcome (OR=6.70; 95% CI, 5.75–7.81; P<0.001). After adjustment, there was no evidence of an effect of PHI on functional outcome (OR=1.01; 95% CI, 0.79–1.28; P=0.96; Table 2). The interaction with prehospital GCS score was not significant (P=0.32), but the effect with extracranial injury was significant: PHI was associated with better functional outcome in patients with higher thorax and abdominal AIS scores (P=0.009 for thorax AIS and P=0.02 for abdominal AIS; Fig. 3).

In-hospital intubation

In the in-hospital analysis, after excluding patients whose tracheas were intubated on scene, 2930 patients were included...
| Age (median [IQR]) | Pre-hospital intubation (n=2846) | Missing (%) | P-value | In-hospital intubation (n=460) | Missing (%) | P-value | In-hospital intubation (n=2470) | Missing (%) | P-value |
|--------------------|-----------------------------------|-------------|---------|---------------------------------|-------------|---------|---------------------------------|-------------|---------|
| 44 [25, 60]        | 52 [33, 68]                       | 0           | <.0001  | 53 [33, 68]                     | 0           | <.0001  | 0.131                           |             |         |
| Male (%)           | 657 [73.8]                        | 2.6         | <.0001  | 134 [72.6]                      | 0           | 0.002   | 0.001                           |             |         |
| Pre-injury ASA physical status | 545 [64.8]                        | 1540 [55.1] | 215 [48.8] | 1368 [56.1] | 0           | <.0001  | 0.001                           |             |         |
| Major* head injury (%) | 851 [95.6]                       | 1960 [68.9] | 441 [95.9] | 1569 [63.5] | 0           | <.0001  | 0.001                           |             |         |
| Major* chest/spine injury (%) | 408 [45.8]                       | 436 [15.3] | 135 [29.3] | 303 [12.3] | 0           | <.0001  | <.0001                          |             |         |
| Major* face injury (%) | 261 [29.3]                       | 341 [12.0] | 106 [23.0] | 237 [9.6] | 0           | <.0001  | 0.001                           |             |         |
| Major* abdominal injury (%) | 139 [15.6]                       | 148 [5.2] | 40 [8.7] | 108 [4.4] | 0           | <.0001  | 0.001                           |             |         |
| Major* extremity injury (%) | 40 [4.5]                        | 45 [1.6] | 12 [2.6] | 33 [1.3] | 0           | 0.067    | <.0001                          |             |         |
| Cause (%)          | 26                     | <.0001     | 2       | 0.105                           |             |         |                                 |             |         |
| Violent injury (%) | 284 [32.7]                       | 1306 [47.0] | 184 [42.3] | 1165 [48.0] | <.0001    | 0.001   |                                 |             |         |
| Major* chest/spine injury (%) | 59 [6.8]                        | 230 [8.3] | 41 [9.4] | 203 [8.4] | 0           | <.0001  | 0.001                           |             |         |
| Major* head injury (%) | 44 [5.3]                        | 186 [6.7] | 37 [8.5] | 155 [6.4] | 0           | <.0001  | 0.001                           |             |         |
| GCS score baseline (median [IQR]) | 4 [3, 8]                        | 15 [13, 15] | 8 [5, 13] | 15 [14, 15] | 2           | <.0001  | <.0001                          |             |         |
| GCS score prehospital (median [IQR]) | 6 [3, 9]                        | 14 [13, 15] | 10 [6, 14] | 15 [14, 15] | 40          | <.0001  |                                 |             |         |
| GCS score at ED arrival (median [IQR]) | 3 [3, 3]                        | 15 [14, 15] | 8 [5, 12] | 15 [14, 15] | 12         | <.0001  |                                 |             |         |
| mGCS score baseline (median [IQR]) | 1 [1, 4]                        | 6 [6, 6] | 5 [1, 6] | 6 [6, 6] | 1           | <.0001  | <.0001                          |             |         |
| mGCS score prehospital (median [IQR]) | 3 [1, 5]                        | 6 [6, 6] | 5 [3, 6] | 6 [6, 6] | 40         | <.0001  |                                 |             |         |
| mGCS score at ED arrival (median [IQR]) | 1 [1, 1]                        | 6 [6, 6] | 5 [1, 6] | 6 [6, 6] | 12         | <.0001  |                                 |             |         |
| Reactive pupils, baseline (%) | 4                     | <.0001     | 5       | <.0001                          |             |         |                                 |             |         |
| Heart rate at ED arrival, mean (so) | 89 [24]                        | 83 [18] | 84 [21] | 82 [17] | 8          | 0.184    |                                 |             |         |
| SBP at ED arrival, mean (so) | 129 [31]                        | 141 [26] | 140 [32] | 141 [25] | 7          | 0.834    |                                 |             |         |
| SpO₂ at ED arrival, median (IQR) | 100 [98, 100]                   | 98 [96, 100] | 98 [96, 100] | 98 [97, 100] | 12         | 0.820    |                                 |             |         |
| Hypoxia at ED (%) | 175 [20.6]                       | 105 [3.9] | 62 [14.9] | 45 [1.9] | 4           | <.0001  | <.0001                          |             |         |
| Hypotension at ED (%) | 189 [22.2]                       | 94 [3.4] | 44 [10.4] | 51 [2.1] | 3           | <.0001  | <.0001                          |             |         |
| EDH (%) | 133 [16.1]                       | 253 [9.6] | 78 [20.0] | 182 [7.8] | 6           | <.0001  | <.0001                          |             |         |
| TSAH (%) | 606 [73.2]                       | 1039 [39.3] | 276 [70.8] | 779 [33.5] | 6          | <.0001  | <.0001                          |             |         |
| Marshall CT class (%) | 77 [9.7]                        | 1143 [44.6] | 35 [9.4] | 1151 [50.9] |            |         |                                 |             |         |
| Visible pathology on CT | 390 [48.9]                       | 968 [37.8] | 135 [36.1] | 850 [37.6] |            |         |                                 |             |         |
| Cisterns present, MLS <5 mm | 110 [13.8]                       | 74 [2.9] | 31 [8.3] | 43 [1.9] |            |         |                                 |             |         |
| Cisterns compressed or absent | 220 [27.6]                       | 376 [14.7] | 173 [46.3] | 217 [9.6] | 0.020      |         |                                 |             |         |
| Arrival time (min) | 20 [11, 30]                       | 15 [10, 27] | 14 [8, 24] | 15 [10, 27] | 44         | 0.009    | 0.009                           |             |         |
| On-scene time (min) | 35 [25, 51]                       | 20 [14, 30] | 23 [15, 32] | 20 [14, 30] | 49         | 0.009    |                                 |             |         |
| Travel time (min) | 20 [12, 35]                       | 16 [10, 25] | 13 [9, 22] | 16 [10, 25] | 49         | 0.009    |                                 |             |         |
ED, patients with a GCS score
Compared with patients whose tracheas were intubated at the
127 (6%) of the patients with a GCS score higher than 8 at ED
ED (41 [46%] of these had GOS-E scores
of 8 or lower at ED arrival had their tracheas intubated at the
intubated at 6 months follow-up.
Of 2458 (84%) patients, a GOS-E was ob-
(Fig. 1). Of these patients, 460 (16%) patients had their tracheas
intubated at the ED. Of 2458 (84%) patients, a GOS-E was ob-
median arrival time was 18 min (IQR, 10
In this IHI subset, 140 (65%) of the patients with a GCS score of
or lower at ED arrival had their tracheas intubated at the
of these had GOS-E scores <4 at 6 months), and
the ED. On average, they had lower baseline GCS score (Fig. 2).
In addition, they were more often male, had a higher propor-
tion of major head injury, and a higher proportion of major
were smaller when patients with GCS scores above 8 were excluded
Supplementary Table S1). The hospital stay of patients that
required IHI was characterised by a longer total length of stay,
and a longer ICU stay, and more days of mechanical ventilation
and sedation. In addition, pneumonia was observed more often in these patients, and more extracranial
surgery, including decompressive craniectomies. Although
the absolute ICP value in patients in whom it was measured
did not differ substantially on average, the therapy intensity
that they received was higher in patients who required intub-
Finally, the blood glucose concentrations were higher
in patients who required intubation, both at day 1 as during
the entire stay.
Before adjusting for confounders, IHI was associated with
worse functional outcome (OR=6.13; 95% CI, 5.05–7.44;
P<0.001). After adjustment, there was no conclusive evidence
of an effect of IHI functional outcome (OR=0.86; 95% CI, 0.65–1.13; P=0.28; Table 2). The interaction with extracranial
injury was not significant, but the effect with GCS score was
significant (P=0.01): IHI was associated with better functional outcome in patients with GCS scores of 10 or lower at ED
arrival (Fig. 3).
Prehospital vs in-hospital intubation
Compared with patients whose tracheas were intubated at the
ED, patients with a GCS score ≤9 whose tracheas were intu-
bated on scene were younger, had more extracranial injuries,
had lower prehospital GCS scores, had more unreactive pupils,
and suffered more from secondary insults. Moreover, the
median arrival time was 18 min (IQR, 10–29), the median on-
scene time was 30 min (IQR, 20–45), and the median travel
time to the hospital was 18 min (IQR, 11–30; Table 1). The
The intubation rates ranged from 0% to 60% for PHI, and from
2% to 56% for IHI (Supplementary Fig. S1). Higher adjusted
intubation rates per hospital were associated with higher mean GOS-E scores (Fig. 4). The relationship was not significa-
dently different for PHI or IHI (P=0.34): for every 10% increase in PHI rate, the mean GOS-E increased with 0.12 (95% CI, 0.01–0.22; P=0.04), whereas for every 10% increase in IHI rate, the
mean GOS-E increased with 0.19 (95% CI, 0.08–0.30; P=0.03).
Discussion
This study aimed to provide insight into the effect of intuba-
tion on outcome in TBI patients. We performed a patient-level
analysis, which is complicated because patients whose tra-
cheas were intubated had sustained more severe trauma. Af-
ter adjustment for possible confounders, there was no
evidence for an overall effect of intubation on functional
outcome in TBI patients. Although higher or lower GCS scores
did not influence the effect of intubation in the prehospital
setting, intubation at the ED seemed to have a more beneficial
effect in patients with lower GCS scores. In contrast, higher
extracranial injury AIS scores mainly influenced the effect of
intubation in the prehospital setting, where intubation was
associated with better functional outcome in patients with
higher extracranial injury AIS scores. The findings of the RCT
by Bernard and colleagues were not reinforced by our results:
PHI was not associated with better functional outcome than
IHI. Finally, higher adjusted intubation rates per centre were
associated with better functional outcomes.
At the patient level, previous observational studies that
assessed the effect of intubation on outcome primarily coun-
terintuitively showed a harm of intubation. Observational
studies are inherently prone to confounding bias. In an
attempt to adjust for this bias, some recent studies used pro-

tensity score matching. These studies also showed an
association of intubation with unwanted outcomes in severe TBI patients: these studies found worsened admission oxygenation and even higher mortality. A postintubation
ICP or occurrence of hypotension could increase mortality.
However, interpreting this relationship as causal is not
appropriate, because the purpose of intubation is to secure
oxygenation. Rather, these studies are more likely to suffer
from residual confounding bias. Our study extensively cor-
rected for potential confounders, which resulted in a large
apparent change in the effect of intubation before and after
adjustment. Although the effect of intubation was not statisti-
cally significant overall, the effect of intubation, especially at
the ED, appeared more likely to be beneficial than harmful.
This is in accordance with a study by Davis and colleagues. This
study found a small positive effect of intubation when
adjusted for Trauma Score and Injury Severity Score (TRISS).
This effect was particularly found in patients who would
otherwise be expected to die: those with a very high TRISS
score. The finding of a more beneficial effect for more severely

**Table 2** Effect of prehospital (PHI) and in-hospital intubation (IHI) on lower functional outcome (GOS-E). An odds ratio greater than 1 indicates a higher probability of lower functional outcome (harmful). For sex, baseline GCS, pupil reactivity, heart rate/systolic blood pressure/saturation at arrival, AIS scores of head/spine/abdominal/face regions, traumatic subarachnoid haemorrhage, epidural haematoma, CT class, hypoxia/hypotension at the emergency department. Only in patients with GCS <9, who received intubation. GCS, Glasgow Outcome Scale; GOS-E, Glasgow Outcome Scale – Extended.

| Intubation | Unadjusted | Adjusted* |
|------------|------------|-----------|
| PHI        | 6.70 (5.75–7.81) | 1.01 (0.79–1.28) |
| IHI        | 6.13 (5.05–7.44) | 0.86 (0.65–1.13) |
| PHI vs IHI | 0.87 (0.66–1.15) | 0.90 (0.65–1.23) |
Fig 3. Treatment effect estimates on functional outcome, allowing for interaction of intubation with GCS score, head AIS, and abdominal AIS. The left panel shows the results for prehospital intubation (PHI), and the right for in-hospital intubation (IHI). The effect is displayed for the statistically average patient, with the median (continuous) or mode (categorical) for all other characteristics. AIS, abbreviated injury severity; GCS, Glasgow Coma Scale.
intubation in patients with a GCS score of 8 or lower. However, based on the current study, shifting the ‘intubation threshold’ to a GCS score of 10 or lower (especially at the ED) could be considered.

PHI was not found to be more beneficial than IHI, in contrast to the findings of Bernard and colleagues. On one hand, it is possible that our results are biased by confounding by indication and hence may not have been able to demonstrate the beneficial effect of PHI. On the other hand, the benefit of PHI demonstrated in an Australian setting by Bernard and colleagues might not directly be generalisable to Europe. In Europe, the density of hospitals is higher, which probably results in shorter prehospital times: the travel time (time from departure from scene until arrival in a hospital) in particular was 10 min shorter in CENTER-TBI. The advantage of prehospital vs IHI is that the airway is secured at an earlier phase. In Europe, the difference in time between a secured airway because of PHI vs IHI might be too small to observe a benefit of PHI: the risks of intubating in a less-controlled environment might not be outweighed by the benefits of an earlier secured airway. This hypothesis, however, should be confirmed.

Higher rates of intubation were associated with more favourable outcome. However, this result is not directly applicable to patient-level decision making. Because of ecological bias, it should rather be explained by differences in resources. These differences in resources contribute to the large variation in intubation rates. Therefore, this finding should stimulate support in improving current European trauma systems, especially in terms of coverage in appropriate intubation.

A limitation of our study is the observational aspect of our study. In the context of an observational study, it cannot be assumed that confounding bias is entirely corrected for using covariate adjustment. There remains a possibility of unmeasured confounding, which is difficult to overcome. For PHI, in particular, we were not able to adjust for prehospital physiology. Therefore, we recommend future observational studies in this field to meticulously register prehospital physiology, including end-tidal CO2. Nevertheless, the estimates for in-hospital and PHI change similarly after adjustment, which supports our conclusion. The lack of details in the prehospital setting drives another limitation, because it complicates the adjustment for GCS score. For PHI, we adjust for the best prehospital GCS score. However, the most appropriate GCS score to account for the effect of intubation is the GCS score before intubation. There might be some subtle differences in adjustment that might have been missed because of that lack of details.

The size and international aspect of our study support generalisability. Our study also suggests a more liberal GCS threshold score of 10 min shorter in CENTER-TBI. The advantage of prehospital vs IHI is that the airway is secured at an earlier phase. In Europe, the difference in time between a secured airway because of PHI vs IHI might be too small to observe a benefit of PHI: the risks of intubating in a less-controlled environment might not be outweighed by the benefits of an earlier secured airway. This hypothesis, however, should be confirmed.

Higher rates of intubation were associated with more favourable outcome. However, this result is not directly applicable to patient-level decision making. Because of ecological bias, it should rather be explained by differences in resources. These differences in resources contribute to the large variation in intubation rates. Therefore, this finding should stimulate support in improving current European trauma systems, especially in terms of coverage in appropriate intubation.

A limitation of our study is the observational aspect of our study. In the context of an observational study, it cannot be assumed that confounding bias is entirely corrected for using covariate adjustment. There remains a possibility of unmeasured confounding, which is difficult to overcome. For PHI, in particular, we were not able to adjust for prehospital physiology. Therefore, we recommend future observational studies in this field to meticulously register prehospital physiology, including end-tidal CO2. Nevertheless, the estimates for in-hospital and PHI change similarly after adjustment, which supports our conclusion. The lack of details in the prehospital setting drives another limitation, because it complicates the adjustment for GCS score. For PHI, we adjust for the best prehospital GCS score. However, the most appropriate GCS score to account for the effect of intubation is the GCS score before intubation. There might be some subtle differences in adjustment that might have been missed because of that lack of details.

The size and international aspect of our study support generalisability. Our study also suggests a more liberal GCS score threshold should perhaps influence decisions regarding tracheal intubation, especially when considering PHI.

Conclusions

At the systems level, higher intubation rates are associated with better functional outcome. This finding probably reflects that more resourced trauma systems have better outcomes. This finding warrants support for developing trauma systems throughout Europe.

At the patient level, intubation does not seem to be associated with better or worse outcome in the general TBI population. However, in more severely injured patients, intubation
was associated with better functional outcome. Moreover, patients with TBI and significant extracranial injury seemed to benefit most from PHI, whereas the impact of ED intubation was most influenced mostly by GCS score. In addition, in this multicentre study, PHI was not associated with better functional outcome than IHI for patients with TBI.

Authors’ contributions
Conceptualisation: BYG, MK
Data curation: BYG
Formal analysis: BYG
Investigations: BYG, CAS, DN, AM, FL, HFL
Methodology: BYG, DN, MK, HFL
Project administration: BYG, MK, HFL
Software acquisition: BYG
Supervision: MK, HFL
Validation of the results: BYG
Writing of the original draft: BYG, CAS, FL, MK, HFL
Visualisation: BYG, CAS

Declarations of interest
The authors declare that they have no conflicts of interest.

Funding
European Union 7th Framework Program (EC Grant 602150). Additional funding from Hannelore Kohl Stiftung (Germany), OneMind (USA), and Integra LifeSciences Corporation (USA). The funders had no role in the study design, enrolment, collection of data, writing, or publication decisions.

Acknowledgements
The CENTER-TBI participants and investigators: Cecilia Åkerlund1, Kristzina Amrein2, Nada Andelic3, Lasse Andreassen4, Audny Anke5, Anna Anton6, Gérard Audibert7, Philippe Azouvi8, Maria Luisa Azzolini9, Ronald Bartels10, Pal Barzó11, Romuald Beauvais12, Ronny Beer13, Bo-Michael Bellander14, Antonio Belli15, Han Benali16, Maurizio Berardino17, Luigi Beretta9, Morten Blaabjerg18, Peter Bragge19, Alexandra Braziunaite50, Vibeke Brinck21, Joanne Brooker22, Camilla Brorsson23, Andreas Buki24, Monika Bullinger25, Manuel Cabeleira26, Alessio Caccioppol27, Emiliana Calap27, Maria Rosa Calvi2, Peter Cameron28, Guillermo Carbayo Lozano29, Marco Carbonara27, Simona Cavallo17, Giorgio Chevallard30, Arturo Chierogeto30, Giuseppe Citerio31,32, Iriss Ceyisakar33, Hans Clusmann34, Mark Coburn35, Jonathan Coles36, Jamie D. Cooper37, Marta Correia38, Amra Covec39, Nicola Curry40, Endre Czetei3, Marek Czosnyka26, Claire Dahyot-Fizelier41, Paul Dark42, Helen Dawes43, Véronique De Keyser44, Vincent Degos45, Francesco Della Porta46, Hugo den Boogert47, Bart Depreitere48, Dula Dilvesi, Abhishek Dixit48, Emma Donoghue49, Jens Dreier49, Guy-Loup Dutille45, Ari Ercole48, Patrick Esser43, Erzsébet Ezer51, Martin Fabricius51, Valery L. Feigin51, Kelly Foks51, Shirin Frisvold51, Alexander Furmanov54, Pablo Gagliardi55, Damien Galanaud16, Dashiell Ganter45, Guoyi Gao58, Pradeep George59, Alexandre Ghuysen60, Lele Giola61, Ben Glocker62, Jago Golubovic63, Pedro A. Gomez63, Johannes Gratze64, Benjamin Gravesteijn33, Francesca Grossi45, Russell L. Grues65, Deepak Gupta66, Juana A. Haagsma67, Iain Haitsma68, Raimund Helbok69, Eirik Helseth68, Lindsay Hortos69, Jilski Huisjes66, Peter J. Hutchinson70, Bram Jacobs70, Stefan Jankowski72, Mike Jarrett71, Jr-yao Jiang78, Fayen Johnson77, Kelly Jones73, Maarten Karan67, Angelos G. Kolias68, Erwin Kompanje74, Daniel Kondziella72, Evgenios Koraropoulos88, Lars-Owe Koskinen79, Noemi Kovacs79, Ana Kowark35, Alfonso Lagares69, Linda Lanyon59, Steven Laureys77, Fiona Lecky78,79, Didier Ledoux77, Rolf Lefering80, Valerie Legrand81, Aurelie Lejeune82, Leon Levi83, Roger Lightfoot84, Hester Lingsma85, Andrew L R. Maas86, Ana M. Castano-Leon86, Marc Maegel87, Marek Majdan89, Alex Manara90, Geoffrey Manley91, Costanza Martino90, Hugues Marechal92, Julia Mattern93, Catherine McMahon95, Bela Melegh96, David Menon97, Tomas Menovsky94, Ana Mikolic95, Benoit Misset96, Visakh Muraleedharan97, Lynnette Murray98, Ancuta Negrui99, David Nelson100, Virginia Newcombe99, Daan Nieboer101, Jozsef Nyriradi102, Otsile Olubu103, Matej Oresic104, Fabiozzi Ortolano107, Arnau Palote107, Paul M. Farizel108, Jean-François Payen109, Natasha Perera112, Vincent Perilarg110, Paolo Perona111, Wilco Peul112, Anna Pippop-Karjalainen113, Matti Pirinen114, Horia Pjes115, Suzanne Polinder116, Ingo Pomposo117, Jussi P. Posti118, Louis Puybasset119, Andrea Rados120, Arminas Raguaukas121, Rahul Raj101, Malinka Rambagala122, Jonathan Rhodes127, Sylvia Richardson128, Sophie Richter42, Samuli Ripatti43, Saulius Rocka105, Cecilie Roe109, Olav Roise110,111, Jonathan Rosand112, Jeffrey V. Rosenfeld113, Christina Rosenlund114, Guy Rosenthal115, Rolf Rossain116, Sandra Rossi99, Daniel Rueckert102, Martin Rusnak115, Juan Sahuquillo104, Oliver Sakowitz116,117, Renan Sanchez-Porras116,118, Janos Sandor117, Nadine Schafe10, Silke Schmidt118, Herbert Schoechl119, Guus Schoonman,120, Rico Frederik Schou121, Elisabeth Schwendenschein121, Charlie Sewall34, Toril Skandsen122,123, Peter Smielewski26, Abayomi Sorinola124, Emmanuel Stamatakis31,48, Simon Stanson40, Robert Stevens125, William Stewart126, Ewout W. Steyerberg33,27, Nino Stocchetti128, Nina Sundstrom129, Anneliese Synnot22,23,30, Riikka Takala131, Viktoria Tamás124,125, Tomas Tamosiuni126, Mark Steven Taylor129, Braden Te Ao129, Olli Tenovuo100,112, Alice Theadom53, Matt Thomas86, Dick Tibboel130,131, Marjoleen Timmers27,54, Christos Tobias124, Tony Trapani107, Cristina Maria Tudora92, Peter Vajkoczy135, Shirley Vallance28, Eglis Valeinis126, Zoltán Vámoss11, Mathieu van der Jagt136, Gregory Van der Steen44, Joukje van der Naalt71, Jeroen T. J. M. van Dijck100, Thomas A. van Essen100, Wim Van Hecke137, Caroline van Heugten138, Dominique Van Praagh139, Thijs Vande Vyvere140, Roel P. J. van Wijk100, Alessia Vargiuoli122, Emmanuel Vega53, Kimberley Velt33, Jan Verheyden137, Paul M. Vespa140, Anne Vink121,141, Rimantas Vilcinis132, Victor Volovici67, Nicole von Steinbuchel139, Daphne Voormolen123, Petar Vulekovic126, Kevin K. W. Wang122, Eveline Wiegers33, Guy Williams132, Lindsay Willso119, Stefan Winzeck141, Stefan Wolf142, Zhihui Xiang143.

1Department of Physiology and Pharmacology, Section of Perioperative Medicine and Intensive Care, Karolinska Institutet, Stockholm, Sweden
2Janos Szentagothai Research Centre, University of Pécs, Pécs, Hungary
Division of Surgery and Clinical Neuroscience, Department of Physical Medicine and Rehabilitation, Oslo University Hospital and University of Oslo, Oslo, Norway

Department of Neurosurgery, University Hospital Northern Norway, Tromso, Norway

Department of Physical Medicine and Rehabilitation, University Hospital Northern Norway, Tromso, Norway

Trauma Surgery, Medical University Vienna, Vienna, Austria

Department of Anesthesiology & Intensive Care, University Hospital Nancy, Nancy, France

Department of Anesthesiology & Intensive Care, S. Raffaele University Hospital, Milan, Italy

Department of Neurosurgery, Radboud University Medical Center, Nijmegen, Netherlands

Department of Neurosurgery, University of Szeged, Szeged, Hungary

International Projects Management, ARTTIC, Munich, Germany

Department of Neurology, Neurological Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria

Department of Neurosurgery & Anesthesia & Intensive Care Medicine, Karolinska University Hospital, Stockholm, Sweden

NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, UK

Anesthesie-Réanimation, Assistance Publique – Hôpitaux de Paris, Paris, France

Department of Anesthesia & ICU, AOU Città della Salute e della Scienza di Torino – Orthopedic and Trauma Center, Turin, Italy

Department of Neurology, Odense University Hospital, Odense, Denmark

BehaviourWorks Australia, Monash Sustainability Institute, Monash University, Victoria, Australia

Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia

Quesgen Systems Inc., Burlingame, CA, USA

Australian & New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

Department of Surgery and Perioperative Science, Umeå University, Umeå, Sweden

Department of Neurosurgery, Medical School, University of Pécs, Hungary and Neurotrauma Research Group, János Szentágothai Research Centre, University of Pécs, Pécs, Hungary

Department of Medical Psychology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

Brain Physics Lab, Division of Neurosurgery, Dept of Clinical Neurosciences, University of Cambridge, Addenbrooke’s Hospital, Cambridge, UK

Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

ANZIC Research Centre, Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Victoria, Australia

Department of Neurosurgery, Hospital of Cruces, Bilbao, Spain

NeuroIntensive Care, Niguarda Hospital, Milan, Italy

School of Medicine and Surgery, Università Milano Bicocca, Milano, Italy

NeuroIntensive Care, ASST di Monza, Monza, Italy

Department of Public Health, Erasmus Medical Center-University Medical Center, Rotterdam, Netherlands

Department of Neurosurgery, Medical Faculty RWTH Aachen University, Aachen, Germany

Department of Anaesthesiology, University Hospital of Aachen, Aachen, Germany

Department of Anesthesia & Neurointensive Care, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK

School of Public Health & PM, Monash University and The Alfred Hospital, Melbourne, Victoria, Australia

Radiology/MRI department, MRC Cognition and Brain Sciences Unit, Cambridge, UK

Institute of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany

Oxford University Hospitals NHS Trust, Oxford, UK

Intensive Care Unit, CHU Poitiers, Poitiers, France

University of Manchester NIHR Biomedical Research Centre, Critical Care Directorate, Salford Royal Hospital NHS Foundation Trust, Salford, UK

Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK

Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium

Department of Anesthesiology & Intensive Care, Maggiore Della Carità Hospital, Novara, Italy

Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium

Department of Neurosurgery, Clinical centre of Vojvodina, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

Division of Anaesthesia, University of Cambridge, Addenbrooke’s Hospital, Cambridge, UK

Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Intensive Care Unit, CHR Citadelle, Liège, Belgium

Department of Anaesthesiology and Intensive Therapy, University of Pécs, Pécs, Hungary

Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Region Hovedstaden Righospitalet, Copenhagen, Denmark

National Institute for Stroke and Applied Neurosciences, Faculty of Health and Environmental Studies, Auckland University of Technology, Auckland, New Zealand

Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands

Department of Anesthesiology and Intensive Care, University Hospital Northern Norway, Tromso, Norway

Department of Neurosurgery, Hadassah-hebrew University Medical center, Jerusalem, Israel

Fundación Instituto Valenciano de Neurorehabilitación (FIVAN), Valencia, Spain

Department of Neurosurgery, Shanghai Renji hospital, Shanghai Jiaotong University/School of Medicine, Shanghai, China

Karolinska Institutet, INCF International Neuroinformatics Coordinating Facility, Stockholm, Sweden

Emergency Department, CHU, Liège, Belgium
61 Neurosurgery clinic, Pauls Stradins Clinical University Hospital, Riga, Latvia
62 Department of Computing, Imperial College London, London, UK
63 Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain
64 Department of Anesthesia, Critical Care and Pain Medicine, Medical University of Vienna, Vienna, Austria
65 College of Health and Medicine, Australian National University, Canberra, Australia
66 Department of Neurosurgery, Neurosciences Centre & JPN Apex Trauma Centre, All India Institute of Medical Sciences, New Delhi, India
67 Department of Neurosurgery, Erasmus MC, Rotterdam, Netherlands
68 Department of Neurosurgery, Oslo University Hospital, Oslo, Norway
69 Division of Psychology, University of Stirling, Stirling, UK
70 Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke’s Hospital & University of Cambridge, Cambridge, UK
71 Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
72 Neurointensive Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
73 Salford Royal Hospital NHS Foundation Trust Acute Research Delivery Team, Salford, UK
74 Department of Intensive Care and Department of Ethics and Philosophy of Medicine, Erasmus Medical Center, Rotterdam, Netherlands
75 Department of Clinical Neuroscience, Neurosurgery, Umeå University, Umeå, Sweden
76 Hungarian Brain Research Program – Grant No. KTIA_13_NAP-A-II/8, University of Pécs, Pécs, Hungary
77 Cyclotron Research Center, University of Liège, Liège, Belgium
78 Centre for Urgent and Emergency Care Research (CURE), Health Services Research Section, School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
79 Emergency Department, Salford Royal Hospital, Salford, UK
80 Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany
81 VP Global Project Management CNS, ICON, Paris, France
82 Department of Anesthesiology-Intensive Care, Lille University Hospital, Lille, France
83 Department of Neurosurgery, Rambam Medical Center, Haifa, Israel
84 Department of Anesthesiology & Intensive Care, University Hospitals Southampton NHS Trust, Southampton, UK
85 Cologne-Merheim Medical Center (CMMC), Department of Traumatology, Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany
86 Intensive Care Unit, Southmead Hospital, Bristol, Bristol, UK
87 Department of Neurological Surgery, University of California, San Francisco, CA, USA
88 Department of Anesthesiology & Intensive Care, M. Bufalini Hospital, Cesena, Italy
89 Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany
90 Department of Neurosurgery, The Walton centre NHS Foundation Trust, Liverpool, UK
91 Department of Medical Genetics, University of Pécs, Pécs, Hungary
92 Department of Neurosurgery, Emergency County Hospital Timisoara, Timisoara, Romania
93 School of Medical Sciences, Orebro University, Orebro, Sweden
94 Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland
95 Analytic and Translational Genetics Unit, Department of Medicine; Psychiatric & Neurodevelopmental Genetics Unit, Department of Psychiatry; Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
96 Program in Medical and Population Genetics; The Stanley Center for Psychiatric Research, The Broad Institute of MIT and Harvard, Cambridge, MA, USA
97 Department of Radiology, University of Antwerp, Edegem, Belgium
98 Department of Anesthesiology & Intensive Care, University Hospital of Grenoble, Grenoble, France
99 Department of Anesthesiology & Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy
100 Department of Neurosurgery, Leiden University Medical Center, Leiden, Netherlands and Department of Neurosurgery, Medical Center Haaglanden, The Hague, Netherlands
101 Department of Neurosurgery, Helsinki University Central Hospital, Helsinki, Finland
102 Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Injury Centre, Turku University Hospital and University of Turku, Turku, Finland
103 Department of Anesthesiology and Critical Care, Pitié-Salpêtrière Teaching Hospital, Assistance Publique, Hôpitaux de Paris and University Pierre et Marie Curie, Paris, France
104 Neurotraumatology and Neurosurgery Research Unit (UNINN), Vall d’Hebron Research Institute, Barcelona, Spain
105 Department of Neurosurgery, Kaunas University of technology and Vilnius University, Vilnius, Lithuania
106 Department of Neurosurgery, Rezekne Hospital, Rezekne, Latvia
107 Department of Anaesthesia, Critical Care & Pain Medicine NHS Lothian & University of Edinburgh, Edinburgh, UK
108 Director, MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, UK
109 Department of Physical Medicine and Rehabilitation, Oslo University Hospital/University of Oslo, Oslo, Norway
110 Division of Orthopedics, Oslo University Hospital, Oslo, Norway
111 Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
112 Broad Institute, Cambridge MA Harvard Medical School, Boston MA, Massachusetts General Hospital, Boston, MA, USA
113 National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, Victoria, Australia
114 Department of Neurosurgery, Odense University Hospital, Odense, Denmark
115 International Neurotrauma Research Organisation, Vienna, Austria
116 Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany
117 Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Debrecen, Debrecen, Hungary
118 Department Health and Prevention, University Greifswald, Greifswald, Germany
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.05.067.

References

1. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol 2017; 16: 987–1048

2. Majdan M, Plancikova D, Brazinova A, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. Lancet Public Health 2016; 1: e76–83

3. booksmedicosorg. Advanced trauma life support ATLS, 9th Edn.

4. Green RS, Butler MB, Erdogan M. Increased mortality in trauma patients who develop postintubation hypotension. J Trauma Acute Care Surg 2017; 83: 569–74

5. Manley G. Hypotension, hypoxia, and head injury. Arch Surg 2001; 136: 1118–23

6. Badjatia N, Carney N, Crocco TJ, et al. Guidelines for prehospital management of traumatic brain injury, 2nd edition. Prehosp Emerg Care 2008; 12(Suppl 1): 51–52

7. Carney N, Totten AM, Hawryluk GWJ, et al. Guidelines for the management of severe traumatic brain injury, 4th edition. Neurosurgery 2017; 80: 6–15

8. Shafi S, Gentilello L. Pre-hospital endotracheal intubation and positive pressure ventilation is associated with hypotension and decreased survival in hypovolemic trauma patients: an analysis of the National Trauma Data Bank. J Trauma 2005; 59: 1140–4. discussion 1145–7

9. Burney RG, Winn R. Increased cerebrospinal fluid pressure during laryngoscopy and intubation for induction of anesthesia. Anesth Analg 1975; 54: 687–90

10. Davis DP, Meade W, Sise MJ, et al. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J Neurotrauma 2009; 26: 2217–23

11. Davis D, Dunford J, Poste J, et al. The impact of hypoxia and hyperventilation on outcome after paramedic rapid sequence intubation of severely head-injured patients. J Trauma Inj Infect Crit Care 2004; 57: 1–10

12. Marmarou A, Anderson RL, Ward JD, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg 1991; 75: 559–66

13. Stocchetti N, Maas AIR. Traumatic intracranial hypertension. N Engl J Med 2014; 370: 2121–30

14. Badjatia N, Carney N, Crocco TJ, et al. Guidelines for prehospital management of traumatic brain injury prehospital guidelines. 2nd Edn. New York: Brain Trauma Foundation; 2006

15. Bernard SA, Nguyen V, Cameron P, et al. Prehospital rapid sequence intubation improves functional outcome for patients with severe traumatic brain injury. Ann Surg 2010; 252: 959–65

16. Davis DP, Aguilar S, Sonnleitner C, Cohen M, Jennings M. Latency and loss of pulse oximetry signal with the use of digital probes during prehospital rapid-sequence intubation. Prehosp Emerg Care 2011; 15: 18–22

17. Cnossen MC, Polinder S, Lingsma HF, et al. Variation in structure and process of care in traumatic brain injury:
provider profiles of European Neurotrauma Centers participating in the CENTER-TBI study. PLoS One 2016; 11: 1–21

18. Cnossen MC, Scholten AC, Lingsma HF, et al. Adherence to guidelines in adult patients with traumatic brain injury: a living systematic review. J Neurotrauma 2016; 14 [Epub ahead of print].

19. Franschman G, Peerdeman SM, Greuters S, et al. Pre-hospital endotracheal intubation in patients with severe traumatic brain injury: guidelines versus reality. Resuscitation 2009; 80: 1147–51

20. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007; 335: 806–8

21. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European neurotrauma effectiveness research in traumatic brain injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery 2015; 76: 67–80

22. Steyerberg EW, Wiegers E, Sewalt C, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. Lancet Neurol 2019; 18: 923–34

23. Weir J, Steyerberg EW, Butcher I, et al. Does the extended Glasgow outcome scale add value to the conventional Glasgow outcome scale? J Neurotrauma 2012; 29: 53–8

24. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med 2008; 5: 1251–61

25. Davis DP, Peay J, Sise MJ, et al. Prehospital airway and ventilation management: a trauma score and injury severity score-based analysis. J Trauma Inj Infect Crit Care 2010; 69: 294–301

26. Pape M, Giannakopoulos GF, Zuidema WP, et al. Is there an association between female gender and outcome in severe trauma? A multi-center analysis in The Netherlands. Scand J Trauma Resusc Emerg Med 2019; 27: 16

27. Buuren S van. Flexible imputation of missing data. Boca Raton, FL: CRC Press; 2018

28. Gravesteijn BY, Sewalt CA, Ercole A, et al. Variation in the practice of tracheal intubation in Europe after traumatic brain injury: a prospective cohort study. Anaesthesia 2020; 75: 45–53

29. Von Elm E, Schoettker P, Henzi I, Osterwalder J, Walder B. Pre-hospital tracheal intubation in patients with traumatic brain injury: systematic review of current evidence. Br J Anaesth 2009; 103: 371–86

30. Haltmeier T, Benjamin E, Siboni S, Dilektasli E, Inaba K, Demetriades D. Prehospital intubation for isolated severe blunt traumatic brain injury: worse outcomes and higher mortality. Eur J Trauma Emerg Surg 2017; 43: 731–9

31. Karamanos E, Talving P, Skiada D, et al. Is prehospital endotracheal intubation associated with improved outcomes in isolated severe head injury? A matched cohort analysis. Prehosp Disaster Med 2014; 29: 32–6

32. Spaite DW, Hu C, Bobrow BJ, et al. Association of out-of-hospital hypotension depth and duration with traumatic brain injury mortality. Ann Emerg Med 2017; 70: 522–30

33. Davis DP, Heister R, Poste JC, Hoyt DB, Ochs M, Dunford JV. Ventilation patterns in patients with severe traumatic brain injury following paramedic rapid sequence intubation. Neurocrit Care 2005; 2: 165–71

34. Gaither JB, Spaite DW, Bobrow BJ, et al. Balancing the potential risks and benefits of out-of-hospital intubation in traumatic brain injury: the intubation/hyperventilation effect. Ann Emerg Med 2012; 60: 732–6

35. Warner KI, Cuschieri J, Copass MK, Jurkovich GJ, Bulger EM. The impact of prehospital ventilation on outcome after severe traumatic brain injury. J Trauma Inj Infect Crit Care 2007; 62: 1330–6

36. Chi JH, Knudson MM, Vassar MJ, et al. Prehospital hypoxia affects outcome in patients with traumatic brain injury: a prospective multicenter study. J Trauma 2006; 61: 1334–41

37. Benjamin E, Haltmeier T, Chouliaras K, et al. Witnessed aspiration in trauma: frequent occurrence, rare morbidity—a prospective analysis. J Trauma Acute Care Surg 2015; 79: 1030–6

38. Greenland S, Morgenstern H. Ecological bias, confounding, and effect modification. Int J Epidemiol 1989; 18: 269–74

Handling editor: Michael Avidan