Intracranial pressure monitors associated with increased venous thromboembolism in severe traumatic brain injury

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Abstract
Background Utilization of intracranial pressure monitors (ICPMs) has not been consistently shown to improve mortality in patients with severe traumatic brain injury (TBI). A single-center analysis concluded that venous thromboembolism (VTE) chemoprophylaxis (CP) posed no significant bleeding risk in patients following ICPM implementation; however, there is still debate about the optimal use and timing of CP in patients with ICPMs for fear of worsening intracranial hemorrhage. We hypothesized that ICPM use is associated with increased time to VTE CP and thus increased VTE in patients with severe TBI.

Methods A retrospective analysis of the Trauma Quality Improvement Program (2010–2016) was performed to compare severe TBI patients with and without ICPMs. A multivariable logistic regression analysis was completed.

Results From 35,673 patients with severe TBI, 12,487 (35%) had an ICPM. Those with ICPMs had a higher rate of VTE CP (64.3% vs. 49.4%, \( p < 0.001 \)) but a longer median time to CP initiation (5 vs. 4 days, \( p < 0.001 \)) as well as a longer hospital length of stay (LOS) (18 vs. 9 days, \( p < 0.001 \)) compared to those without ICPMs. After adjusting for covariates, ICPM use was found to be associated with a higher risk of VTE (9.2% vs 4.3%, OR = 1.75, CI = 1.42–2.15, \( p < 0.001 \)).

Conclusions Compared to patients without ICPMs, those with ICPMs had a longer delay to initiation of CP leading to an increase in VTE. In addition, there was a nearly two-fold higher associated risk for VTE in patients with ICPMs even when controlling for known VTE risk factors. Improved adherence to initiation of CP in the setting of ICPMs may help decrease the associated risk of VTE with ICPMs.

Keywords Traumatic brain injury · Intracranial pressure monitor · Venous thromboembolism · Prophylaxis

Introduction

Each year approximately 2.5 Mio. people visit the emergency department for traumatic brain injury (TBI), leading to over 280,000 hospitalizations and 56,000 deaths [1]. In cases of severe TBI with elevated intracranial pressure (ICP), evaluation and management may involve the insertion of invasive intracranial devices such as an intracranial pressure monitor (ICPM), which can serve to monitor the ICP alone and/or therapeutically drain the cerebral spinal fluid. However, the use of ICPM is associated with increased risk of venous thromboembolism (VTE) chemoprophylaxis (CP) posed no significant bleeding risk in patients following ICPM implementation; however, there is still debate about the optimal use and timing of CP in patients with ICPMs for fear of worsening intracranial hemorrhage. We hypothesized that ICPM use is associated with increased time to VTE CP and thus increased VTE in patients with severe TBI.

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Compared to patients without ICPMs, those with ICPMs had a longer delay to initiation of CP leading to an increase in VTE. In addition, there was a nearly two-fold higher associated risk for VTE in patients with ICPMs even when controlling for known VTE risk factors. Improved adherence to initiation of CP in the setting of ICPMs may help decrease the associated risk of VTE with ICPMs.

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fluid (e.g. external ventricular drain) [2]. Despite the ability to monitor and adjust treatment based on the ICPM, use of these devices has not been shown to improve mortality in multiple previous studies [2–4]. One study found no benefit in the use of an ICPM compared to clinical examination plus imaging in patients without an ICPM [5]. Both the Brain Trauma Foundation and American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) guidelines recommend the use of ICPMs for patients with Glasgow Coma Scale (GCS) ≤ 8 and an abnormal computed tomography (CT) scan. The ACS TQIP guidelines recommend the use of the modified Berne-Northwood criteria to determine the optimal timing for venous thromboembolism (VTE) chemoprophylaxis (CP) in the setting of ICPMs. This criteria takes into consideration the stability of a patient’s CT scan as well as risk factors for hemorrhage [6]. For patients with severe TBI but a stable head CT scan, the recommendation is to start VTE CP within 24–72 h, whereas there remains ambiguity towards this timing when an ICPM is used as not all physicians are mandated to follow ACS TQIP guidelines.

Severe TBI increases the risk for VTE as a result of inappropriate thrombosis caused by the systemic release of tissue factor from brain parenchyma, hypercoagulability, and prolonged immobilization [7]. However, VTE CP is sometimes delayed or avoided in patients with ICPM due to physician discretion in balancing the risk of postprocedural hemorrhage with possible VTE events [8]. A recent single-center analysis concluded that VTE CP did not pose a significant bleeding risk in patients following ICPM implementation, but there is still no accepted standard for its optimal use or timing [8]. The rate of VTE in TBI patients with an ICPM is reported to be up to 25% despite receiving mechanical prophylaxis (compression stockings and/or intermittent pneumatic compression and venous pumps), and can be up to 50% in patients without mechanical prophylactic measures [10, 11]. In contrast, a systematic review of the literature on VTE CP in TBI patients revealed no significant difference in VTE events for individuals who received early (< 3 days) versus late (> 3 days) CP [12]. However, other studies have shown that delayed initiation of VTE CP is associated with increased risk of VTE events [13–15]. We hypothesized that patients with severe TBI and ICPMs would have delayed the initiation of VTE CP and, therefore, increased risk of VTE compared to those without an ICPM.

Methods

This was a retrospective analysis using the TQIP database. We queried TQIP from January 2013 to December 2016 to identify all adult patients admitted with severe TBI. This was defined by an abbreviated injury scale (AIS) grade > 3 for the head. Those that died within 24-h or that had non-survivable TBI (AIS head grade = 6) were excluded. Patients with ICPMs were compared to those without ICPMs. The four types of ICPMs included within the TQIP database are: (1) Intraparenchymal oxygen monitor (e.g. Licox), (2) intraparenchymal pressure monitor (e.g. Camino bolt, subarachnoid bolt, intraparenchymal catheter), (3) intraventricular drain/catheter (e.g. ventriculostomy, external ventricular drain) and (4) jugular venous bulb. Our primary end-point of interest was the development of VTE including deep vein thrombosis (DVT) or pulmonary embolism (PE). Other measured outcomes include the total hospital length of stay (LOS), intensive care unit (ICU) LOS, ventilator days, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), pneumonia, and mortality. The number of trauma surgeons and neurosurgeons per center as well as packed red blood cell (PRBC) transfusions within 24 h were also recorded. In addition, we determined which patients were started with VTE CP and how many days after admission this was initiated. VTE CP included either unfractionated heparin (UFH) or low-molecular-weight-heparin (LMWH).

Patient demographic information including age, gender, and pre-hospital comorbidities including disseminated cancer, congestive heart failure (CHF), end stage renal disease (ESRD), smoking, diabetes, hypertension, chronic obstructive pulmonary disease (COPD), and cerebrovascular accident (CVA) were collected. The injury profile included the injury severity score (ISS), AIS for body region, lowest systolic blood pressure (SBP) within 24-h, midline shift (> 5 mm), and pupil reactivity.

Descriptive statistics were performed for all variables. A Mann–Whitney–U test was used to compare continuous variables and Chi-square test was used to compare categorical variables for bivariate analysis. We assessed the distribution of continuous variables by measuring skewness and kurtosis. Categorical data were reported as percentages, and continuous data were reported as medians with interquartile range. The continuous variables were not normally distributed and, therefore, we only included the median and IQR.

The magnitude of the association between predictor variables and the development of VTE was first measured using a univariable logistic regression model. Covariates with \( p \leq 0.20 \) were included in a hierarchical multivariable logistic regression model and the adjusted risk of VTE was reported with an odds ratio (OR) and a 95% confidence interval (CI). We additionally tested for multicollinearity using the variance inflation factor (VIF). The VIF of all covariates were less than 5 with the highest one being 1.16 for midline shift on CT scan. We also performed a subgroup analysis in patients with only severe head injuries (AIS head > 3) and no other severe injuries (extracranial AIS grades \( \leq 3 \) for face, neck, spine, thorax, abdomen, upper and lower extremities).
All p-values were two-sided, with a statistical significance level of <0.05.

We computed interaction terms which comprised of (1) ARDS and pneumonia, and (2) ARDS and intubation. We also made interaction terms using the integral or continuous variables by first standardizing them or centering the variable. This allowed us to create a new interaction variable which was computed as a product of two centered continuous integral variables. These included (3) ISS and AIS-spine, (4) ISS and AIS-thorax, (5) ISS and AIS-abdomen, and (6) ISS and AIS-lower extremity. The predictor variables were chosen based on a discussion among coauthors and a review of the literature [8–16]. Covariates with statistical significance (p < 0.20) were included in a hierarchical multivariable logistic regression model and the adjusted risk of mortality was reported. All analyses were performed with IBM SPSS Statistics for Windows (Version 24, IBM Corp., Armonk, NY).

Results

Demographics and primary outcome

From 35,673 patients with severe TBI, 12,487 (35.0%) received an ICPM and 23,186 (65.0%) did not. Compared to those without ICPMs, the ICPM group was younger (median age, 36 vs. 46 years old, p < 0.001), had a higher ISS (median 29 vs 26, p < 0.001), and was found to have lower rates of disseminated cancer (0.2% vs 0.5%, p < 0.001), CHF (1.2% vs 2.3%, p < 0.001), ESRD (0.5% vs 1.1%, p < 0.001), diabetes (6.9% vs 9.8%, p < 0.001), hypertension (15.0% vs 23.5%, p < 0.001), COPD (3.2% vs 4.5%, p < 0.001), and CVA (1.1% vs 2.3%, p < 0.001) (Table 1). The ICPM group had a higher rate of DVT (8.0% vs 3.6%, p < 0.001) and PE (1.8% vs 1.0%, p < 0.001) (Table 2).

Risk of VTE in severe TBI with and without ICPMs

On univariable analysis, ICPM use was found to have higher risk for VTE (OR 2.24, CI 2.05–2.44, p < 0.001) (Table 3). After correcting for covariates in a multivariable logistic regression model, those with ICPMs continued to have higher risk for VTE (OR 1.75, CI 1.42–2.15, p < 0.001). The strongest independent risk factor for VTE was VTE CP (OR 3.90, CI 2.92–5.20, p < 0.001) followed by pneumonia (OR 1.95, CI 1.50–2.53, p < 0.001) and AIS-spine grade > 3 (OR 1.89, CI 1.12–3.17, p < 0.05) (Table 4).

After computing the interaction for the multivariable model in patients with and without ICPMs, the Mcfadden’s Pseudo-R-squared change was 0.019 with a significance of 0.003, suggesting an improvement of 1.9% (Table 4).

Subgroup analyses

Ventriculostomy drains are different than other types of ICPMs in the fact that they also may serve a therapeutic purpose to patients with elevated ICP. For this reason, we ran an additional multivariable analysis comparing patients with intraventricular drain/catheters to those with intraparenchymal monitors and found no difference between the two in risk of VTE (OR 0.90, CI 0.68–1.18, p = 0.45).

Multivariable logistic regression analysis of patients with isolated TBI for risk of VTE controlling the same covariates included in Table 4 revealed that ICPMs continue to be associated with an increased risk of VTE (OR 1.93, CI 1.52–2.44, p < 0.001).

We ran a subgroup analysis on patients with ICPM receiving either LMWH or UFH. The majority of patients received LMWH (58.7% vs. 41.3%). Compared to those receiving UFH, those receiving LMWH were younger (median age, 36 vs. 41, p < 0.001) with a higher median ISS (29 vs. 26, p < 0.001). Those receiving LMWH had lower rates of CHF (41.6% vs. 58.4%, p < 0.001), ESRD (15.8% vs. 84.2%, p < 0.001), and diabetes (6.4% vs. 9.1%, p < 0.001), compared to those receiving UFH. The LMWH cohort had a similar rate of VTE (8.9% vs. 9.6%, p = 0.114) but lower rate of death (8.7% vs. 17.8%, p < 0.001). On multivariable logistic regression analysis, the adjusted risk of VTE was similar among both groups (OR 0.98, CI 0.65–1.34, p = 0.211). After adjusting for age ≥ 65, ISS ≥ 25, sex, obesity, midline shift, DM, COPD, CHF, cirrhosis, ESRD, hypotension on arrival, tachypnea on arrival, tachycardia on arrival, severe-AIS-spine, severe-AIS-thorax, severe-AIS-abdomen and severe-AIS-lower extremity, patients receiving LMWH had a lower associated risk of mortality (OR 0.48, 0.41–0.57, p < 0.001) compared to those receiving UFH.

And finally, we performed an analysis on only patients that received VTE chemoprophylaxis and found that the risk of VTE in patients with ICP monitors continues to be increased (OR 1.57, CI 1.25–1.98, p < 0.001). Furthermore, in the subgroup that received VTE CP, the risk of VTE continues to increase stepwise with increase in the number of days to starting prophylaxis (≥ 5 days OR 1.63, CI 1.31–2.04; ≥ 6 days OR 1.92, CI 1.54–2.39; ≥ 7 days OR 1.97, CI 1.57–2.47).

Clinical outcomes

Compared to patients without ICPMs, patients with ICPMs had a longer ICU LOS (13 days vs 5 days, p < 0.001), more ventilator days (10 days vs 4 days, p < 0.001), and longer total hospital LOS (18 days vs 9 days, p < 0.001) as well as a higher rate of mortality (33.6% vs 31.1%, p < 0.001) (Table 2). After adjusting for age ≥ 65, ISS ≥ 25, sex, obesity, midline shift, DM, COPD, CHF, cirrhosis, ESRD,
hypotension on arrival, tachypnea on arrival, tachycardia on arrival, severe-AIS-spine, severe-AIS-thorax, severe-AIS-abdomen and severe-AIS-lower extremity, patients with ICPM had a similar associated risk of mortality (OR 0.91, 0.83–1.00, \( p = 0.056 \)) compared to patients without ICPM. The ICPM group did have a higher proportion of patients receiving VTE CP (64.3% vs 49.4%, \( p < 0.001 \)), but also experienced a greater delay in initiating VTE CP (5 days vs 4 days, \( p < 0.001 \)) (Table 2) with a greater risk of VTE with each additional delayed day to CP (OR 1.63 at 5 days, CI 1.31–2.04; OR 1.92 at 6 days, CI 1.54–2.39; OR 1.97 at 7 days, CI 1.57–2.47, \( p < 0.001 \)) (Table 4). The ICPM group also had increased risk of AKI (2.7% vs 1.8%, \( p < 0.001 \)), ARDS (5.5% vs 2.8%, \( p < 0.001 \)), and pneumo-

### Table 1 Demographics of adult trauma patients with severe traumatic brain injury

| Characteristic                        | – ICP monitor (\( n = 23,186 \)) | +ICP monitor (\( n = 12,487 \)) | \( p \) value |
|---------------------------------------|-----------------------------------|---------------------------------|---------------|
| Age, year, median (IQR)               | 46.0 (36)                         | 36.0 (30)                       | <0.001        |
| Male, \( n (%) \)                     | 16,973 (72.9%)                    | 9655 (76.6%)                    | <0.001        |
| ISS, median (IQR)                     | 26.0 (13)                         | 29.0 (13)                       | <0.001        |
| Lowest SBP within 24 h, median (IQR)  | 77.0 (48)                         | 84.0 (44)                       | <0.001        |
| Comorbidities, \( n (%) \)           |                                   |                                 |               |
| Disseminated cancer                   | 113 (0.5%)                        | 24 (0.2%)                       | <0.001        |
| Congestive heart failure              | 541 (2.3%)                        | 144 (1.2%)                      | <0.001        |
| End-stage renal disease               | 263 (1.1%)                        | 68 (0.5%)                       | <0.001        |
| Smoker                                | 3671 (15.8%)                      | 1948 (15.6%)                    | 0.67          |
| Diabetes                              | 2277 (9.8%)                       | 859 (6.9%)                      | <0.001        |
| Hypertension                          | 5472 (23.5%)                      | 1875 (15.0%)                    | <0.001        |
| COPD                                  | 1048 (4.5%)                       | 396 (3.2%)                      | <0.001        |
| Cerebrovascular accident              | 543 (2.3%)                        | 134 (1.1%)                      | <0.001        |
| Midline shift (\( > 5 \) mm), \( n (%) \) | 2604 (38.5%)                     | 1691 (43.4%)                    | <0.001        |
| Pupil(s) reactive, \( n (%) \)       |                                   |                                 |               |
| One                                   | 458 (10.8%)                       | 457 (18.0%)                     | <0.001        |
| Neither                               | 2470 (39.6%)                      | 1310 (38.7%)                    | 0.38          |
| AIS (grade > 3), \( n (%) \)         |                                   |                                 |               |
| Spine                                 | 476 (2.0%)                        | 166 (1.3%)                      | <0.001        |
| Thorax                                | 2399 (10.3%)                      | 1839 (14.7%)                    | <0.001        |
| Abdomen                               | 760 (3.3%)                        | 518 (4.1%)                      | <0.001        |
| Upper extremity                       | 15 (0.1%)                         | 8 (0.1%)                        | 0.99          |
| Lower extremity                       | 386 (1.7%)                        | 316 (2.5%)                      | <0.001        |
| Total beds > 600, \( n (%) \)        | 10,774 (46.3%)                    | 6059 (48.5%)                    | <0.001        |
| Trauma surgeons, \( n (%) \)         |                                   |                                 |               |
| 1–6                                   | 10,827 (46.5%)                    | 5361 (42.9%)                    | <0.001        |
| \( \geq 7 \)                          | 12,449 (53.5%)                    | 7126 (57.1%)                    | <0.001        |
| Neurosurgeons, \( n (%) \)           |                                   |                                 |               |
| 1–2                                   | 1570 (6.7%)                       | 939 (7.5%)                      | <0.05         |
| \( \geq 3 \)                          | 21,706 (93.3%)                    | 11,548 (92.5%)                  | <0.05         |

ACS American college of surgeons, PAAI penetrating abdominal aortic injury, ISS injury severity score, IQR interquartile range, SBP systolic blood pressure, AIS abbreviated injury scale

### Discussion

TBI has a significant morbidity and mortality including an increased risk of VTE. The results of this study support our hypothesis that ICPM use is associated with increased risk of VTE in patients with severe TBI. This risk appears to increase with greater delay in initiating CP as demonstrated by greater than 30% increase in VTE with the initiation of VTE chemoprophylaxis on day five compared to day four of hospitalization.

A delay in VTE CP has been shown to be associated with increased risk for VTE in patients with TBI. Even when delaying CP > 7 days, the study by Kwiatt et al. demonstrated substantial risk of intracranial hemorrhage.
Table 2  Clinical outcomes and related factors in adult trauma patients with severe traumatic brain injury

| Outcome                                      | – ICP monitor (n = 23,186) | + ICP monitor (n = 12,487) | P value |
|----------------------------------------------|-----------------------------|-----------------------------|---------|
| LOS, days, median (IQR)                      | 9.0 (15)                    | 18.0 (21)                   | < 0.001 |
| ICU days, median (IQR)                       | 5.0 (9)                     | 13.0 (14)                   | < 0.001 |
| Ventilator, days, median (IQR)               | 4.0 (7)                     | 10.0 (11)                   | < 0.001 |
| PRBC transfusion ≥ 6 units within 4 h        | 910 (3.9%)                  | 630 (5.0%)                  | < 0.001 |
| VTE CP, n (%)                                | 11,295 (49.4%)              | 7897 (64.3%)                | < 0.001 |
| Days to CP, median (IQR)                     | 4.0 (3)                     | 5.0 (5)                     | < 0.001 |

Complications, n (%)

| Acute kidney injury                          | 409 (1.8%)                  | 332 (2.7%)                  | < 0.001 |
| ARDS                                         | 661 (2.8%)                  | 686 (5.5%)                  | < 0.001 |
| VTE                                           |                             |                             |         |
| Deep vein thrombosis                         | 837 (3.6%)                  | 999 (8.0%)                  | < 0.001 |
| Pulmonary embolism                           | 227 (1.0%)                  | 227 (1.8%)                  | < 0.001 |
| Pneumonia/VAP                                | 2938 (12.6%)                | 3347 (26.8%)                | < 0.001 |
| Mortality, n (%)                             | 7241 (31.1%)                | 4201 (33.6%)                | < 0.001 |

ICP intracranial pressure, LOS length of stay, IQR interquartile range, ICU intensive care unit, VTE venous thromboembolism, ARDS acute respiratory distress syndrome, VTE venous thromboembolism, VAP ventilator-associated pneumonia

Table 3  Univariable analysis of risk factors for venous thromboembolism in adult severe traumatic brain injury

| Risk factor                                    | OR    | CI               | P value |
|------------------------------------------------|-------|-----------------|---------|
| ICP monitor                                    | 2.24  | 2.05–2.44       | < 0.001 |
| VTE CP                                         | 4.66  | 4.15–5.25       | < 0.001 |
| Time to CP                                     |       |                 |         |
| ≥ 5 days                                       | 1.72  | 1.56–1.90       | < 0.001 |
| ≥ 6 days                                       | 1.88  | 1.71–2.07       | < 0.001 |
| ≥ 7 days                                       | 1.96  | 1.77–2.16       | < 0.001 |
| Age ≥ 65                                       | 0.67  | 0.61–0.74       | < 0.001 |
| Male                                           | 1.34  | 1.24–1.45       | < 0.001 |
| ISS ≥ 25                                       | 1.41  | 1.31–1.52       | < 0.001 |
| Disseminated cancer                            | 0.82  | 0.48–1.41       | 0.48    |
| PRBC transfusion ≥ 6 units within 4 h          | 1.73  | 1.47–2.05       | < 0.001 |
| Obesity (BMI ≥ 30 kg/m²)                       | 1.44  | 1.31–1.58       | < 0.001 |
| Midline shift (> 5 mm)                         | 0.74  | 0.62–0.88       | < 0.05  |
| Pupil one reactive                             | 1.06  | 0.80–1.41       | 0.68    |
| Pupil neither reactive                         | 0.56  | 0.46–0.69       | < 0.001 |
| Intubated                                      | 1.92  | 1.64–2.24       | < 0.001 |
| Acute kidney injury                            | 2.51  | 2.15–2.93       | < 0.001 |
| Acute respiratory distress syndrome            | 2.23  | 2.01–2.49       | < 0.001 |
| Pneumonia/VAP                                  | 3.84  | 3.59–4.10       | < 0.001 |
| Pelvis fracture                                | 1.70  | 1.55–1.87       | < 0.001 |
| Abbreviated injury scale- spine (grade > 3)    | 1.88  | 1.56–2.28       | < 0.001 |
| Abbreviated injury scale- thorax (grade > 3)   | 1.85  | 1.70–2.01       | < 0.001 |
| Abbreviated injury scale- abdomen (grade > 3)  | 2.08  | 1.82–2.39       | < 0.001 |
| Abbreviated injury scale- lower extremity (grade > 3) | 2.17  | 1.79–2.62       | < 0.001 |
| Smoker                                         | 1.13  | 1.03–1.24       | < 0.05  |

ICP intracranial pressure, VTE venous thromboembolism, ISS injury severity score, VAP ventilator-associated pneumonia
progression in up to 14.9% of patients, demonstrating that
the risk of progression may be independent of when CP is
initiated [13]. Conversely, more recent reports including a
systematic review by Jamjoom et al. of randomized trials
and cohort studies demonstrated that when early CP < 72 h
was performed, no increase in progression of intracranial
hemorrhage was seen along with a decrease in VTE events
compared to late CP [14]. The Neurocritical Care Society
suggests that an ideal start time for VTE CP is sometime
less than 72 h after a hemorrhage, but admits that the exist-
ing literature is limited with no definitive guidelines [15].
One study recommends initiating prophylaxis 24 h after a
stable intracranial hemorrhage (ICH), but this study is lim-
ited by a small sample size, and remaining studies that rec-
ommend starting up to 4 days after a stable ICH are lim-
ited by lack of randomization or a comparator group [15,
17]. Therefore, we performed a post hoc analysis starting
at five days after injury to see if delays beyond this con-
servative initiation point were associated with increased
risk of VTE. Our study demonstrated that ICPMs are
associated with longer delay to CP initiation leading to
increased VTE. Those with ICPMs had a delayed start
time for VTE CP by an entire day. We found that even
a single day of delayed VTE CP led to an increased risk
of VTE. Our findings add to the current literature that
delayed initiation of VTE CP leads to increased incidence
of VTE. We demonstrated that ICPM use can influence the
timing of starting the CP in a way that ultimately leads to
increased occurrence of VTE. In addition, our subgroup
analysis of patients with isolated TBI revealed an even
higher association between ICPM placement and VTE
regardless of chemoprophylaxis timing. We thus believe
that the increased risk of VTE should be considered when
deciding on the ICPM placement. In addition, our findings
highlight the need for future research and the development
of consensus guidelines regarding the timing of initiation
of VTE CP in the setting of ICPM use.

Although ICPMs are placed to closely evaluate a patient
with severe TBI, there appears to be no mortality benefit due
to these devices. Retrospective studies by Kostić et al. and
Shaﬁ et al. had a combined total of 2031 patients and both
reported no signiﬁcant improvement in mortality with ICPM
use [2, 9]. Furthermore, the benchmark evidence from the
South American trials: treatment of intracranial pressure, a

| Risk factor | OR   | CI     | P value |
|-------------|------|--------|---------|
| ICP monitor | 1.75 | 1.42–2.15 | < 0.001 |
| VTE CP      | 3.90 | 2.92–5.20  | < 0.001 |
| Time to CP  |      |         |         |
| ≥ 5 days    | 1.63 | 1.31–2.04  | < 0.001 |
| ≥ 6 days    | 1.92 | 1.54–2.39  | < 0.001 |
| ≥ 7 days    | 1.97 | 1.57–2.47  | < 0.001 |
| Age ≥ 65    | 0.86 | 0.63–1.18  | 0.35    |
| Male        | 1.31 | 1.01–1.69  | < 0.05  |
| ISS ≥ 25    | 1.25 | 0.96–1.63  | 0.11    |
| PRBC transfusion ≥ 6 units within 4 h | 1.34 | 0.89–2.04 | 0.17 |
| Obesity (BMI ≥ 30 kg/m²) | 1.08 | 0.87–1.35 | 0.50 |
| Midline shift (> 5 mm) | 0.95 | 0.76–1.19 | 0.68 |
| Pupil neither reactive | 0.76 | 0.60–0.95 | < 0.05 |
| Intubated   | 1.99 | 0.87–4.54  | 0.10    |
| Acute kidney injury | 1.39 | 0.81–2.37 | 0.23 |
| Acute respiratory distress syndrome | 1.11 | 0.72–1.73 | 0.63 |
| Pneumonia/VAP | 1.95 | 1.50–2.53 | < 0.001 |
| Pelvis fracture | 1.35 | 0.78–2.36 | 0.29 |
| Abbreviated injury scale- spine (grade > 3) | 1.89 | 1.12–3.17 | < 0.05 |
| Abbreviated injury scale- thorax (grade > 3) | 0.92 | 0.64–1.31 | 0.63 |
| Abbreviated injury scale- abdomen (grade > 3) | 1.62 | 1.05–2.52 | < 0.05 |
| Abbreviated injury scale- lower extremity (grade > 3) | 1.85 | 1.17–2.91 | < 0.05 |
| Smoker      | 0.86 | 0.65–1.13  | 0.27    |

ICP intracranial pressure, VTE venous thromboembolism, ISS injury severity score, PRBC packed red blood cells, BMI body mass index, VAP ventilator-associated pneumonia

Interaction terms: (1) ARDS and pneumonia (2) ARDS and intubation (3) ISS and AIS-spine (4) ISS and AIS-thorax (5) ISS and AIS-abdomen (6) ISS and AIS-lower extremity (pseudo-R-squared change 0.019, p < 0.003)
randomized prospective multicenter study, found that ICP monitoring with a goal < 20 mm Hg to have no benefit in terms of mortality compared to treatment based on clinical examination and imaging [5]. They also found no significant difference in functional and cognitive status or 6-month mortality. Our study not only revealed no mortality benefit, but also demonstrated an overall increased mortality for those with ICPMs. However, after adjusting for demographics, injury severity, condition on arrival, and comorbidities, patients with ICPM had a similar associated risk of mortality compared to patients without ICP monitors. We found that those with ICPMs also had higher rates of complications such as AKI, ARDS, and VTE. That said, caution regarding these findings is necessary as patients with ICPM were older and had higher injury severity scores; thus, the difference in mortality may be related to these factors and not the placement of an ICPM. Regardless, the lack of mortality benefit evidenced by our study and several others coupled with the increased rates for complications for which CP may be taken into consideration when deciding to place an ICPM. Our findings support the need for a well-designed, large multicenter randomized controlled trial that addresses not only the potential benefits of ICPM use but also the potential complications associated with its use such as VTE and mortality.

The use of LMWH versus UFH for VTE prophylaxis has been debated due to the lower cost of UFH. In the prospective randomized clinical trial conducted by Geerts et al., the LMWH, enoxaparin at a dose of 30 millig twice daily, was compared to 5,000 units of UFH every 12 h rather than the accepted dosage schedule of every 8 h [18]. This fueled discussion and disagreement on the use of LMWH versus UFH in trauma patients due to the inaccuracy of the dosage studied. This dispute was addressed in a large retrospective analysis of over 18,000 patients conducted by Jacobs et al., which found that as compared to UFH, LMWH was associated with decreased risk of mortality, VTE, PE, and DVT when accounting for risk adjustments [19]. Another study by Benjamin et al. of over 20,000 patients concluded that LMWH was an independent protective factor against mortality and VTE regardless of VTE chemoprophylaxis timing in patients with TBI [20]. This study similarly found that our patient population had decreased associated risk for mortality with the use of LMWH as compared to UFH; however, interestingly we found that the associated risk of VTE was similar between both the groups. Without a significant difference in the associated risk of VTE it might suggest that LMWH may have an effect on mortality that is not related to VTE and indicates the need for a large prospective study to definitively determine if and what benefit LMWH may have over properly dosed UFH.

One particular unexpected finding in our analysis was that the increased risk of VTE associated with VTE CP in patients with severe TBI. This is likely not a true finding as there is no reason to believe that administration of CP would increase the risk of VTE. We believe this is a limitation of this database as there is selection bias at play: those patients at highest risk of VTE were started with CP whereas a subset of patients who may have a severe TBI as defined by their AIS, but were clinically well and thus discharged prior to when CP would be initiated. Furthermore, since this is an index hospitalization database, any patient who may have been discharged prior to CP and return with a VTE would not have been included.

This retrospective database study has a number of limitations including those inherent to the use of a large database such as inaccurate reporting of data, missing data, and unavailable pertinent data variables. For instance, there is no data regarding whether VTE CP was held during placement, removal and/or during ICPM use or for any other reasons such as operations or ongoing hemorrhage. Also, there is no data regarding the dosage of CP as some studies have demonstrated improved outcomes based on the agent as well as weight based regimens [14]. In addition, there is no ability to determine the rationale for the placement of an ICP monitor, and there is an inability to track whether physicians remained adherent to brain trauma foundation or ACS TQIP guidelines. Furthermore, the timing of the VTE event and whether the VTE occurred prior to placement, during use, or after removal of the ICPM is not available within the database. Similarly, we are unable to account for any association with non-pharmacologic VTE prophylaxis such as ambulation or mechanical compression devices. Finally, a significant limitation is that there are no data regarding intracranial hemorrhage progression while on VTE CP.

**Conclusion**

In a severe TBI population, ICPM use was found to be associated with a longer time to initiation of CP leading to an increase in VTE. In addition, there was a nearly two-fold increased associated risk of VTE even when controlling for known VTE risk factors. Given the lack of clear benefit for ICPMs, physicians should weight this risk especially if they are considering holding CP in association with the use of these devices. Future prospective studies might provide evidence-based guidelines regarding VTE CP in the setting of ICPMs as well as confirm our findings regarding increased risk of complications such as VTE associated with ICPM and to determine whether these devices should continue to be recommended.

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Data availability The datasets generated and/or analyzed during the current study are available in the Trauma Quality Improvement Program (2010–2016) website, https://www.facs.org/quality-programs/trauma/tqp/center-programs/tqip

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval Consent to participate in this study was waived off by the international review board as all the study information was deidentified.

Consent for publication Not applicable.

References

1. DeGrauw X, Thurman D, Xu L, et al. Epidemiology of traumatic brain injury-associated epilepsy and early use of anti-epilepsy drugs: an analysis of insurance claims data, 2004–2014. Epilepsy Res. 2018;146:41–9.

2. Kostić A, Stefanović I, Novak V, et al. Prognostic significance of intracranial pressure monitoring and intracranial hypertension in severe brain trauma patients. Med Pregl. 2011;64(9–10):461–5.

3. Haddad S, Aldawood AS, Alferayan A, et al. Relationship between intracranial pressure monitoring and outcomes in severe traumatic brain injury patients. Anaesth Intensive Care. 2011;39(6):1043–50.

4. Shafi S, Diaz-Arrastia R, Madden C, et al. Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. J Trauma. 2008;64(2):335–40.

5. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med. 2013;369(25):2465.

6. ACS TQIP. Best Practices in the Management of Traumatic Brain Injury. 2015

7. Carney N, Totten AM, O’Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017;80(1):6–15.

8. Tavakoli S, Peitz G, Ares W, et al. Complications of invasive intracranial pressure monitoring devices in neurocritical care. J Neurosurg. 2017;124(5):1–9.

9. Dengler AB, Mendez-Gomez P, Chavez A, et al. Safety of chemical DVT prophylaxis in severe traumatic brain injury with invasive monitoring devices. Neurocrit Care. 2016;25(2):215–23.

10. Denson K, Morgan D, Cunningham R, et al. Incidence of venous thromboembolism in patients with traumatic brain injury. Am J Surg. 2007;193(3):380–3.

11. Geerts WH, Code KI, Jay RM, et al. A prospective study of venous thromboembolism after major trauma. N Engl J Med. 1994;331(24):1601–6.

12. Hachem LD, Mansouri A, Scales DC, et al. Anticoagulant prophylaxis against venous thromboembolism following severe traumatic brain injury: a prospective observational study and systematic review of the literature. Clin Neurosurg Neurosurg. 2018;175(68):68–73.

13. Kwiat ME, Patel MS, Ross SE, et al. Is low-molecular-weight heparin safe for venous thromboembolism prophylaxis in patients with traumatic brain injury? A Western Trauma Association multicenter study. J Trauma Acute Care Surg. 2012;73(3):625–8.

14. Jamjoom AA, Jamjoom AB. Safety and efficacy of early pharmacological thromboprophylaxis in traumatic brain injury: systematic review and meta-analysis. J Neurotrauma. 2013;30(7):503–11.

15. Fried HI, Nathan BR, Rowe AS, et al. The Insertion and management of external ventricular drains: an evidence-based consensus statement: a statement for healthcare professionals from the neurocritical care society. Neurocrit Care. 2016;24(1):61–81.

16. Jacobs BN, Cain-Nielsen AH, Jakubus JL, et al. Unfractionated heparin versus low-molecular-weight heparin for venous thromboembolism after major trauma. N Engl J Med. 1996;335:701–7.

17. Jacobs BN, Cain-Nielsen AH, Jakubus JL, et al. Unfractionated heparin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in trauma. J Trauma Acute Care Surg. 2017;83(1):151–8.

18. Benjamin E, Recinos G, Aiolfi A, et al. Pharmacological thromboembolic prophylaxis in traumatic brain injuries: low molecular weight heparin is superior to unfractionated heparin. Ann Surg. 2017;266(3):463–9.