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ORIGINAL SCIENTIFIC REPORT

# Early Chemical Thromboprophylaxis Does not Increase the Risk of Intracranial Hematoma Progression in Patients with Isolated Severe Traumatic Brain Injury

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## Abstract

*Background* Venous thromboembolism (VTE) is recognized as a factor of morbidity and mortality in trauma patients suffering from severe blunt traumatic brain injury (TBI). The administration of pharmacological prophylaxis is broadly accepted as an effective therapy to prevent VTE events in trauma patients. Regardless of its ascertained efficacy, the risk of hematoma progression complicates the therapy in patients suffering from TBI: therefore, the optimal time to start prophylactic anticoagulation in these patients remains controversial.

*Methods* All primary admissions to our level-1-trauma center between January 2012 and December 2016 were screened for severe blunt TBI with a head Abbreviated Injury Scale (AIS) $\geq 3$. Patients who died within the first 24 h were excluded. Basic demographic results, thromboembolic events and progression of the intracranial hematoma were extracted from the patient's records. The patients were categorized into 4 groups according to start of VTE chemoprophylaxis: early ( $< 24$ h after hospitalization), intermediate (24–48 h), late ( $> 48$ h) and no therapy (no prophylactic anticoagulation within the first five days of hospitalization). A total of 292 patients with severe TBI were analyzed (early: $n = 93$, intermediate: $n = 90$, late: $n = 74$, no therapy: $n = 35$). The overall rate of intracranial bleeding progression was 13.6% after prophylactic anticoagulation was started.

*Results* No statistically significant differences were found in the frequency of intracranial bleeding progression comparing the different time groups (early 12.9% vs. intermediate 11.1% vs. late 17.6%; adj. $p = 0.13$). In patients with VTE chemoprophylaxis, no thromboembolic events were recorded. Male gender, age, head AIS and subarachnoidal hemorrhage were identified as independent risk factors associated with intracranial hematoma progression.

*Conclusion* The early administration of VTE chemoprophylaxis within 24 h after admission in patients with severe TBI did not increase the risk of intracranial bleeding progression.

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## Introduction

Traumatic brain injury (TBI) was identified as an independent risk factor for the development of venous thromboembolic events (VTE), which can crucially deteriorate patient outcomes [1, 2]. Rates for patients suffering from isolated TBI to sustain a VTE have been reported as high as 58% [3–5]. Consequently, in trauma patients, prophylaxis against thromboembolic complications is unalterable and has been shown to reduce the rate of VTE, in particular if started within the first 72 h after the injury [4, 6]. The prophylaxis is usually based on mechanical methods, such as deep venous thrombosis (DVT) stockings, on the one hand and a pharmacological therapy, either by unfractionated heparin or low molecular weight heparin (LMWH) on the other. In a recent study by Benjamin et al. [7], the authors were able to demonstrate that chemoprophylaxis with LMWH is superior to unfractionated heparin with regard to survival and prophylactic benefit. However, despite combined mechanical and chemoprophylaxis, the rate of thromboembolic events in TBI patients remains comparatively high [8]. For these reasons, early start of chemoprophylaxis after trauma seems to be of utmost importance. However, in daily clinical practice, the VTE prophylaxis is frequently delayed due to the fear of further progression of the intracranial bleeding.

Guidelines regarding the optimal start point of VTE prophylaxis remain vague; the Brain Injury Association recommends the application of LMWH and mechanical prophylaxis at any time during a TBI patients' clinical course but also emphasizes that pharmacological prophylaxis is a risk factor for intracranial hematoma expansion [9]. As a consequence, due to a lack of precise recommendations, the initiation of VTE chemoprophylaxis is usually based on individual case-by-case decisions or single-center protocols that orientate either on radiographic findings, clinical examinations or the physicians' experience [10, 11].

The goal of the present study was to examine whether the start time of pharmacological VTE prophylaxis has an impact on clinical outcome parameters and intracerebral bleeding progression in patients with isolated severe blunt TBI.

## Material and methods

The medical records of all patients admitted to our level–1–trauma center from January 2013 to December 2016 were screened for the diagnosis of severe blunt TBI. To identify these patients, the clinical documentation system was searched for relevant codes from the International Classification of Diseases (ICD-10) including S02.0, S02.1, S06.2, S06.21, S06.22, S06.23, S06.30, S06.31, S06.33, S06.34, S06.38, S06.4, S06.5, S06.6 and S06.8. ICD-10 codes representing mild TBI were excluded from the search a priori (e.g., S06.0, Concussion). All primary admissions with age $\geq$ 18 years and with an Abbreviated Injury Scale (AIS) Head $\geq$ 3 points, indicating a severe TBI, were included. Patients $<$ 18 years of age, patients who were transferred to another hospital during the first 24 h, deaths within 24 h of admission, patients on palliative care due to the initial severity of the TBI and patients with intracranial bleedings not caused by trauma as well as patients with concomitant injuries in any other body regions with an AIS $\geq$ 2 were excluded.

According to the time point of the first application of VTE chemoprophylaxis (LMWH, enoxaparin), the patients were categorized into 4 groups: early (first administration $<$ 24 h after hospitalization), intermediate (24–48 h) and late ($>$ 48 h), with a fourth group established including patients that did not receive any VTE chemical prophylaxis within the first five days of hospitalization.

Basic data for all patients were abstracted from our institutional patients charts, including information on demographics, injury pattern (AIS scores of the different body regions), clinical management, laboratory findings and outcome.

The time of computed tomography (CT) scan of the head, type of intracranial injury, time and dose of first administration of chemical prophylaxis and type of neurosurgical intervention were retrospectively abstracted. Pre-existing anticoagulation and transfusion requirement was likewise analyzed.

Our institutional management protocol for patients with severe TBI includes a control CT scan of the head six hours after the initial CT scan. Afterward, head CT scans are usually performed on an individual basis whenever there is suspicion of a progression of the intracerebral bleeding (changes in the clinical neurological status).

A progression of the intracerebral bleeding was defined by any increase in the hematoma size in the control CT scan. Thromboembolic events were defined as positive findings on lower extremity Doppler ultrasound for deep venous thrombosis or CT pulmonary angiography for pulmonary emboli (PE). Indications for PE investigation included clinical signs of right ventricular load and fulminant dyspnea. Diagnostics were used in any case with a clinical suspicion for those events.

The primary outcome measure for this study was the occurrence of intracranial bleeding progression. Secondary end-points included thromboembolic events and in-hospital mortality.

This study was approved by the local Committee for Ethics (EV 496/16) of the Johann-Wolfgang Goethe University.

### Statistical analysis

The demographic and clinical characteristics comparing the different time groups (early/intermediate/late/no administration of VTE chemoprophylaxis) were evaluated using bivariate analysis. The $p$ values for categorical variables were derived from the Chi-square or two-sided Fisher's exact test and for continuous variables from the Student's $t$-test or the Mann–Whitney $U$ test. Multivariate analysis was performed to control for confounders diverging significantly ($p < 0.05$) between the compared groups.

To identify risk factors independently associated with progression of the intracranial bleeding, a stepwise logistic regression model was utilized, and risk factors from the bivariate analysis with a $p$-value $< 0.2$ were included in the model.

Values are reported as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. All analyses were performed using the Statistical Package for Social Sciences (SPSS for Mac) version 24.0 (SPSS Inc., Chicago, IL).

## Results

A total of 310 patients met the inclusion criteria. Patients that died within 24 h of admission ($n = 7$) and patients younger than 18 years of age ($n = 11$) were excluded from further analyses (Fig. 1). Consequently, 292 patients suffering from isolated blunt TBI were analyzed. Overall, 65.4% were male, the mean age was 61.8 ± 20.5 years, and the overall $AIS_{head}$ score was 3.6 ± 0.8 points (Table 1). In 93 patients, the VTE prophylaxis was started within 24 h after hospitalization (early group), in 90 patients between 24 and 48 h (intermediate group) and in 74 patients > 48 h (late group). Thirty-five patients did not receive medical VTE prophylaxis for any reason during the first 5 days (no-therapy group) (Fig. 1). Statistically significant differences were found comparing the $AIS_{head}$ scores between the different groups (early vs. intermediate, $p = 0.02$; late vs. no therapy, $p = 0.009$). The frequency of intracerebral bleeding, epidural hematoma, subarachnoidal bleeding and subdural hematoma was comparable between the groups. Fractures of the skull were significantly more often seen in the "early" compared to the "late" cases ($p = 0.002$) and compared to the "no-therapy group" ($p = 0.009$) (Table 1).

Overall, 28% of the patients ($n = 82$) received any pre-injury anticoagulant long-term medication (Table 2). Patients in the "no therapy" and "late group" showed a significantly higher rate of pre-existing anticoagulation compared to patients from the "early group" (early vs. no therapy; $p = 0.036$, early vs. late; $p = 0.01$). No statistically significant differences were found with regard to the administration of packed red blood cells and coagulation factors between the four groups.

In the entire study group, progression of the intracranial bleeding was seen in 45.0% ($n = 132$) of the patients before starting with a VTE chemoprophylaxis and in 13.6% ($n = 35$) of the patients after beginning chemoprophylaxis (Table 3). No statistically significant differences were found in the frequency of intracranial bleeding progression before and after starting the VTE chemoprophylaxis comparing the different time groups (before: adj. $p$-value = 0.211, after: adj. $p$-value = 0.132). Likewise, the in-hospital mortality rate did not differ statistically significant between the "early," "intermediate" and "late" group. No thromboembolic events were observed in those patients that received a VTE chemoprophylaxis. Overall, neurosurgical procedures were performed in 20.2% and were most frequently necessary in the "early" (32.3%) and "intermediate" groups (21.1%). Of the 30 craniectomies that were performed, 24 were due to the initial severity of the TBI and were performed as emergency procedure. The mean time between arrival and beginning of the surgery in

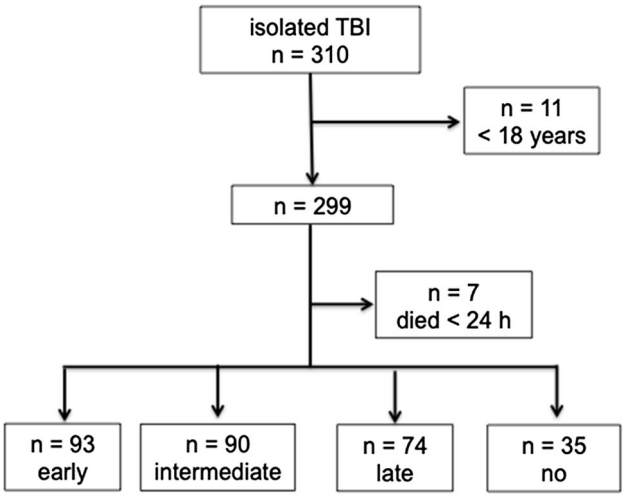


**Fig. 1** Patients were categorized according to the time of first application of pharmacological VTE prophylaxis. Abbreviations: TBI, traumatic brain injury; VTE, venous thromboembolism. Early: initiation of prophylactic anticoagulation < 24 h after admission. Intermediate: initiation of prophylactic anticoagulation between 24–48 h after admission. Late: initiation of prophylactic anticoagulation > 48 h after admission. No: no prophylactic anticoagulation within 5 days after admission

**Table 1** Demographic and injury characteristics in severe TBI patients stratified by the time point of VTE chemoprophylaxis initiation

| | Total ($n$ = 292) | Early ($n$ = 93) | Intermediate ($n$ = 90) | Late ($n$ = 74) | No therapy ($n$ = 35) | $p$-value |
|---|---|---|---|---|---|---|
| Male sex (%) | 65.4 | 61.3 | 66.7 | 71.6 | 60.0 | 0.48 |
| Age (years), mean ± SD | 61.8 ± 20.5 | 62.1 ± 19.1 | 60.8 ± 21.6 | 62.1 ± 21.7 | 64.5 ± 19.3 | 0.84 |
| $AIS_{head}$ (points), mean ± SD | 3.6 ± 0.8 | 3.7 ± 0.8 | 3.6 ± 0.7 | 3.4 ± 0.6 | 3.9 ± 0.9 | 0.004 |
| $AIS_{head}$ 3 (%) | 57.2 | 28.1 | 30.5 | 31.7 | 9.6 | 0.02 |
| $AIS_{head}$ 4 (%) | 25.7 | 34.7 | 34.7 | 20.0 | 10.7 | 0.57 |
| $AIS_{head}$ 5 (%) | 17.1 | 40.0 | 26.0 | 12.0 | 22.0 | 0.01 |
| ICH / contusion (%) | 60.3 | 68.8 | 56.7 | 59.5 | 48.6 | 0.15 |
| SAH (%) | 56.5 | 59.1 | 57.8 | 55.4 | 48.6 | 0.74 |
| SDH (%) | 51.0 | 57.0 | 51.1 | 44.6 | 48.6 | 0.45 |
| EDH (%) | 8.2 | 8.6 | 13.3 | 5.4 | 0 | 0.07 |
| Skull fracture (%) | 46.9 | 60.2 | 46.7 | 36.5 | 34.3 | 0.007 |

*AIS* abbreviated injury scale, *TBI* traumatic brain injury, *ICH* intracerebral hemorrhage, *SAH* subarachnoid hemorrhage, *SDH* subdural hematoma, *EDH* epidural hematoma

**Table 2** Pre-existing anticoagulant medication and therapeutic substitution of blood products and antidotes

| | Total ($n$ = 292) | Early ($n$ = 93) | Intermediate ($n$ = 90) | Late ($n$ = 74) | No therapy ( $n$ = 35) | $p$-value |
|---|---|---|---|---|---|---|
| Pre-existing anticoagulation (%) | 28 | 19.4 | 26.7 | 37 | 37.1 | 0.049 |
| Platelet inhibitor (%) | 21.6 | 15.1 | 21.1 | 28.4 | 25.7 | 0.19 |
| Warfarin (%) | 6.2 | 3.2 | 6.7 | 8.1 | 8.6 | 0.52 |
| NOAC (%) | 1.7 | 1.1 | 2.2 | 2.7 | 0 | 0.71 |
| RBC transfusion (%) | 1.4 | 2.2 | 1.1 | 1.4 | 0 | 0.81 |
| Administration of FFP (%) | 5.5 | 2.2 | 5.6 | 8.1 | 8.6 | 0.31 |
| Administration of PC (%) | 2.1 | 2.2 | 2.2 | 2.7 | 0 | 0.82 |
| Administration of vitamin K (%) | 4.1 | 5.4 | 2.2 | 5.4 | 2.9 | 0.65 |

*NOAC* new oral anticoagulant, *RBC* red blood cell, *FFP* fresh frozen plasma, *PC* platelet concentrate

these patients was 237.1 min ± 181.9 min. None of these patients received VTE prophylaxis prior to surgery. In two of the remaining six patients, surgery was performed due to bleeding progression at a later time (day 4 and day 7, respectively). However, in these 2 patients, VTE prophylaxis was for the first time administered after surgery. Consequently, 4 patients received VTE prophylaxis prior to craniectomy. Indications for surgery in these 4 patients included: development of a chronical subdural hematoma ($n$ = 2; surgery on day 17 and day 20, respectively) and development of a generalized brain edema ($n$ = 2; surgery on day 4 and day 7, respectively). In these four patients, the time between initiation of VTE prophylaxis and operative treatment ranged between 48 and 60 h, respectively.

Various factors potentially associated with a progression of intracranial bleeding after beginning VTE chemoprophylaxis were identified using bivariate analysis. Stepwise logistic regression analysis identified male sex, higher age, $AIS_{head}$ = 5 and subarachnoidal bleeding as independent predisposing risk factors for progression of the intracranial bleeding. The $R^2$ for this model was 0.114.

When analyzing the outcome parameter for the "no-therapy" group separately, the mortality rate (41.2%) was significantly higher compared to all other groups ($p < 0.001$). Furthermore, in the "no-therapy" group, 1 patient (2.9%) presented with a thromboembolic event (deep vein thrombosis). The rate of intracranial hematoma progression in the "no-therapy group" (47.1%) was comparable to those observed in the other groups prior to the initiation of VTE chemoprophylaxis (adj. $p$ = 0.199, adj. OR (95% CI) = 1.19 (0.91–1.54)). Patients in the "no-therapy group" did not receive chemoprophylaxis for following reasons: nine patients did not receive prophylaxis due to the initial severity of the bleeding or spontaneous clinically relevant progression of the hematoma, five patients presented with inherent bleeding disorders, 4 suffered from gastrointestinal bleeding, and 17 patients had

**Table 3** Outcome parameter in patients with severe TBI stratified by the time point of VTE chemoprophylaxis initiation

| | Total ($n$ = 257) | Early ($n$ = 93) | Intermediate ($n$ = 90) | Late ($n$ = 74) | $p$ - value | Adjusted $p$-value[a] | Adjusted OR (95% CI)[a] |
|---|---|---|---|---|---|---|---|
| Bleeding progression, before starting prophylactic anticoagulation (%) | 44.7 | 45.2 | 43.3 | 45.9 | 0.94 | 0.211 | 1.25 (0.88–1.77) |
| Bleeding progression, after starting prophylactic anticoagulation (%) | 13.6 | 12.9 | 11.1 | 17.6 | 0.47 | 0.132 | 1.30 (0.80–2.10) |
| TE event (%) | 0 | 0 | 0 | 0 | – | – | – |
| Mortality (%) | 7.8 | 9.7 | 7.8 | 5.5 | 0.61 | 0.963 | 0.99 (0.51–0.90) |
| Overall neurosurgical intervention (%) | 21.2 | 32.3 | 21.1 | 8.1 | 0.001 | 0.027 | 0.56 (0.34–0.94) |
| ICP-monitoring (%) | 7.8 | 9.7 | 8.9 | 4.1 | 0.36 | 0.725 | 0.89 (0.47–1.70) |
| Craniectomy (%) | 10.1 | 17.2 | 8.9 | 2.7 | 0.008 | 0.036 | 0.49 (0.25–0.95) |

Patients who did not receive chemoprophylaxis during the first five days ("no therapy") were excluded from this analysis

*TE* thromboembolic, *ICP* intracranial pressure, *OR* odds ratio, *CI* confidence interval

[a]adjusted for $AIS_{head}$, skull fracture, pre-existing anticoagulation.

personal directives where therapy was limited to best supportive care (dead > 24 h post admission).

Stratifying the patients according to head AIS score, significantly higher rates of bleeding progression, mortality and neurosurgical interventions were observed (Table 4).

## Discussion

In the present study, the early administration of VTE chemoprophylaxis did not increase the risk of intracranial hematoma progression in patients with isolated TBI. Risk factors associated with bleeding progression after the initiation of VTE chemoprophylaxis included age, male sex, head AIS and subarachnoid bleeding.

Venous thromboembolic events are major complications with potentially fatal consequences following severe TBI. Several studies have shown that TBI is an independent risk factor for the development of DVT [1]. Nevertheless, to date, no clear guidelines exist with regard to the optimal time at which to start VTE chemoprophylaxis. Numerous clinical studies have demonstrated that an early beginning of pharmacotherapy significantly reduces the rate of VTE in TBI patients by approximately 50% [11–13]. However, due to the lack of validated recommendations, the initiation of chemical prophylaxis is currently mainly based on stable bleeding conditions in repeated head CT scans or based on the physicians' clinical experience. The study by Hachem et al. [14] noticed that chemoprophylaxis in severe TBI is often delayed by more than three days after injury. Therefore, the authors claim a standardized multicenter protocol or better prospective randomized studies to further improve the VTE chemoprophylaxis management in this high-risk collective [15]. The latest data from the systematic review of Margolick and colleagues recommend that administering VTE prophylaxis after 24 h following injury may be safe in low-risk TBI patients and stable radiographic findings [16]. In the present study, even in patients with severe TBI, the early administration of LMWH within 24 h did not increase the frequency of bleeding progression compared to the later initiation of VTE chemoprophylaxis.

In our collective, the basic patient data including gender, age and $AIS_{head}$ were similar to previously published results, making our study comparable with those. The overall rate of VTE was low, which is in line with recent studies showing a VTE rate of 0 to 10% in patients with severe head trauma who were treated with chemoprophylaxis [14, 15, 17]. Of note, VTE in our collective was only present in patients not receiving any chemoprophylaxis within the first five days of hospitalization. For TBI patients that did not receive chemoprophylaxis subsequent to TBI, DVT rates of up to 58% were noted, which confirms our own results and indicates the importance of chemical prophylaxis [3, 14]. Likewise, delaying the administration of pharmacological prophylaxis for more than 72 h has been shown to be an independent risk factor for VTE complications and mortality [7]. On the other hand, Scudday et al. [15] demonstrated that administration of VTE chemoprophylaxis during the first 24 h after trauma significantly reduces the rate of VTE events in TBI patients. Bearing these data in mind, it seems reasonable to argue that all trauma patients need a VTE chemical prophylaxis as early as possible in their clinical course.

The main concern associated with an early start of the prophylactic anticoagulation is a progression of the intracranial bleeding. In the literature, the optimal time at which to initiate the prophylaxis has been controversially discussed. A recent retrospective multicenter study, including more than 1200 patients with intracranial hemorrhage, found a hemorrhage progression in 14.5% of

**Table 4** Basic demographic data and outcome parameters in severe TBI patients stratified by the head AIS score

| | AIS 3 ($n$ = 167) | AIS 4 ($n$ = 76) | AIS 5 ($n$ = 49) | $p$-value |
|---|---|---|---|---|
| Male sex (%) | 65.9 | 67.1 | 60.8 | 0.74 |
| Age (years), mean ± SD | 57.9 ± 20.9 | 65.1 ± 20.6 | 70.5 ± 15.9 | < 0.001 |
| Start VTE prophylaxis (hours), mean ± SD | 65 ± 77.1 | 63.4 ± 84.6 | 87 ± 111.1 | 0.24 |
| Bleeding progression, before starting prophylactic anticoagulation (%) | 32.3 | 64.5 | 58.0 | < 0.001 |
| Bleeding progression, after starting prophylactic anticoagulation (%) | 9.6 | 17.3 | 24.0 | 0.02 |
| VTE event (%) | 0 | 0 | 2.0 | 0.09 |
| Mortality (%) | 2.4 | 13.2 | 41.2 | < 0.001 |
| Overall neurosurgical intervention (%) | 5.4 | 28.9 | 56.9 | < 0.001 |

*AIS* abbreviated injury scale, *SD* standard deviation, *VTE* venous thromboembolic

patients after initiating LMWH and was therefore unable to demonstrate the safety of LMWH for VTE prophylaxis in patients with brain injury. The authors consequently concluded that the risk of using LMWH may exceed its benefit. On the contrary, other studies report that early VTE prophylaxis within the first 48 h after trauma is safe if the size of the hematoma in repeated head CT scans remains stable [18, 19]. For low-risk TBI patients (small, stable intracranial bleedings during radiographic controls), Phelan et al. [20] published similar results and subclinical hemorrhage progression rates when comparing patients on Enoxaparin versus those on placebo. Likewise, Frisoli and colleagues report radiographic expansion rates of intracranial hemorrhage in 18% versus 17% in the early (chemoprophylaxis within 24 h) versus the delayed cohort ( > 48 h), respectively [21].

In the present study, 45.9% of patients showed an expansion of the hematoma prior to the beginning of chemoprophylactic therapy. These comparatively high rates might be caused by numerous factors: Patients with isolated severe TBI frequently develop posttraumatic coagulation disorders, which significantly increases the risk of ongoing bleeding in the early phase after trauma [22]. Additionally, a high rate (56.5%) of patients suffered from subarachnoid hemorrhage, which is known to be a strong risk factor for spontaneous hematoma progression [23]. This is further confirmed by our results, where subarachnoid bleeding was identified as an independent risk factor for bleeding progression after the initiation of chemoprophylaxis. Furthermore, in our collective, a high number of patients with pre-existing anticoagulant medication were included. Combining these factors, a significant portion of our cohort has to be classified as high-risk patients with reported progression rates in the literature of almost 60% [24].

In total, 63 patients in our study were on pre-injury antiplatelet medication; however, none of these patients received early platelet transfusion. This is certainly in line with recently published studies demonstrating no beneficial outcome in terms of mortality in platelet-inhibited patients when receiving platelet transfusion [25, 26]. Therefore, our standard in-house therapy includes point-of-care diagnostics including ROTEM® and Multiplate® platelet function analysis, whenever needed. The therapy is subsequently based on these findings as well as the additional routine coagulation parameter.

In contrast, the overall rate of bleeding progression after the onset of pharmaceutical VTE prophylaxis was low (14.1%), indicating that the initiation of prophylaxis was carefully selected. No statistically significant differences were found comparing the early, intermediate and late group. These numbers indicate that even the early initiation of VTE prophylaxis within the first 24 h of the clinical course in patients with severe TBI does not significantly increase the risk of bleeding progression compared to VTE prophylaxis started later. Of note, other studies determined the initiation of chemoprophylaxis between 24 and 72 h to be early [14, 16]. Therefore, we were able to demonstrate that even earlier administration as mentioned above appears to be safe.

Factors that are significantly and independently associated with a bleeding progression included head AIS, subarachnoid hemorrhage, male gender and increasing age. Therefore, these patients need to be monitored carefully for any clinical signs of ongoing bleeding. However, the time of VTE chemoprophylaxis initiation did not prove to be a risk factor for intracranial bleeding progression.

This study has some limitations, most importantly the retrospective nature with all its restrictions to the study design. Furthermore, the diagnosis of VTE was based on clinical symptoms and suspicion, with no routine ultrasound examinations being performed. Therefore, clinically inapparent VTE events may have been missed. Each progression in routine head CT scan follow-ups was recorded, independent from the grade of progression. Therefore, clinically inapparent progressions—which, however, were

recorded radiographically—could result in over-interpretation of the role of the bleeding progression in this study. Furthermore, we are not able to provide any data in regard to the functional outcome of the patients. Finally, this study included patients that underwent surgery and those who did not, introducing a further source of potential bias.

## Conclusion

The early administration of chemoprophylaxis within 24 h after admission in patients with severe blunt TBI did not increase the risk of intracranial bleeding progression. Therefore, our results add to the growing evidence that the early application of pharmacological prophylaxis is safe in these patients.

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**Compliance with ethical standards**

**Conflict of interest** Philipp Störmann, William Osinloye, Thomas M. Freiman, Volker Seifert, Ingo Marzi and Thomas Lustenberger declare that they have no conflict of interest.

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