

Thromboembolic Prophylaxis with Heparin in Patients with Blunt Solid Organ Injuries Undergoing Non-operative Treatment

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Abstract

Background Patients with blunt solid organ injuries (SOI) are at risk for venous thromboembolism (VTE), and VTE prophylaxis is crucial. However, little is known about the safety of early prophylactic administration of heparin in these patients.

Methods This is a retrospective study including adult trauma patients with SOI (liver, spleen, kidney) undergoing non-operative management (NOM) from 01/01/2009 to 31/12/2014. Three groups were distinguished: prophylactic heparin (low molecular weight heparin or low-dose unfractionated heparin) ≤ 72 h after admission ('early heparin group'), >72 h after admission ('late heparin group'), and no heparin ('no heparin group'). Patient and injury characteristics, transfusion requirements, and outcomes (failed NOM, VTE, and mortality) were compared between the three groups.

Results Overall, 179 patients were included; 44.7% in the 'early heparin group,' 34.6% in the 'late heparin group,' and 20.8% in the 'no heparin group.' In the 'late heparin group,' the ISS was significantly higher than in the 'early' and 'no heparin groups' (median 29.0 vs. 17.0 vs. 19.0; $p < 0.001$). The overall NOM failure rate was 3.9%. Failed NOM was significantly more frequent in the 'no heparin group' compared to the 'early' and 'late heparin groups' (10.8 vs. 3.2 vs. 1.3%; $p = 0.043$). In the 'early heparin group' 27.5% patients suffered from a high-grade SOI; none of these patients failed NOM. Mortality did not differ significantly. Although not statistically significant, VTE were more frequent in the 'no heparin group' compared to the 'early' and 'late heparin groups' (10.8 vs. 4.8 vs. 1.3%; $p = 0.066$).

Conclusion In patients with SOI, heparin was administered early in a high percentage of patients and was not associated with an increased NOM failure rate or higher in-hospital mortality.

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Introduction

Non-operative management (NOM) of solid organ injuries (SOI) increased significantly in the last two decades [1]. At present, NOM is an established treatment approach for hemodynamically stable trauma patients with SOI [2, 3].

The risk of failed NOM in trauma patients with SOI, i.e., rebleeding increases with the injury grade, amount of hemoperitoneum, occurrence of an arterio-venous fistula, and contrast extravasation on the computed tomography (CT) scan on admission and decreases over time [4, 5]. Rebleeding rates as high as 32% have been reported in

patients with SOI and contrast extravasation on the CT scan [6]. On the other hand, trauma patients are at risk for venous thromboembolism (VTE) [7, 8]. In orthopedic [9, 10] and elective surgical [11, 12] patients, low molecular weight heparin (LMWH) is currently the standard agent for postoperative VTE prophylaxis.

To date, four studies evaluated postinjury prophylactic heparin administration in trauma patients with blunt SOI [13–16]. However, these studies differed substantially with regard to the study design, patient characteristics, and the time point of heparin administration. Furthermore, only a limited number of patients that received heparin early (within 72 h after hospital admission) were included.

Based on our previous study that assessed prophylactic LMWH administration in trauma patients, a new policy of heparin prophylaxis was introduced at our institution [4]. In patients with any grade of SOI prophylactic LMWH or low-dose unfractionated heparin (LDUH) was administered within 48–72 h after hospital admission, unless patients had contraindications for prophylactic anticoagulation therapy (e.g., traumatic brain injury).

The aim of the current study was to investigate the impact of early prophylactic LMWH or LDUH administration on failed NOM and VTE in patients with liver, splenic, and kidney injuries after the introduction of this new policy.

Methods

Approval for the current study was obtained from the Institutional Revision Board of the Bern University Hospital (KEK 067/14).

Patient selection

This is a retrospective study including adult trauma patients with SOI (liver, spleen, kidney) undergoing non-operative management (NOM) from 01/01/2009 to 31/12/2014. The Bern University Hospital is a tertiary facility that includes a busy trauma center with a yearly admission rate of approx. 500 major trauma patients [Injury Severity Score (ISS) >15].

Inclusion criteria were age >16 years, and blunt SOI with attempted NOM. NOM was defined as no surgery and no angioembolization of the SOI in the first 6 h after hospital admission and was performed in hemodynamically stable patients only. The standard of care for NOM included continuous monitoring of vital signs in the intermediate care or intensive care unit, clinical reevaluation every 6–8 h, and serial hemoglobin levels every 6–8 h.

A surgical or radiological intervention ≥ 6 h after hospital admission was defined as failed NOM. Patients that

died during the first 72 h after hospital admission were excluded.

Data collection

Data were retrospectively collected using the institutional trauma registry [Trauma Audit and Research Network (TARN) database] and electronic patient records. Data collection included type and time of prophylactic heparin (LMWH or LDUH) administration, patient characteristics (sex, age), injury characteristics [Abbreviated Injury Scale (AIS; head, chest, abdomen, extremities, and external), Injury Severity Score (ISS), Glasgow Coma Scale (GCS)], the injured solid organ (liver, spleen, kidney, and pancreas), presence of hemoperitoneum (on abdominal CT scans, massive hemoperitoneum defined as blood in all four quadrants), hypotension at emergency department admission (systolic blood pressure <90 mmHg), hollow organ injuries, severe pelvic or lower extremity fractures (AIS extremities ≥ 3), transfused blood products in the 24 h after admission [packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelets (PLT)], risk factors for failed NOM, and outcome variables (in-hospital mortality, VTE, and failed NOM).

Risk factors for failed NOM were defined as follows: high-grade injuries, contrast extravasation, pseudoaneurysm, massive hemoperitoneum, and vessel truncation [4, 6, 13].

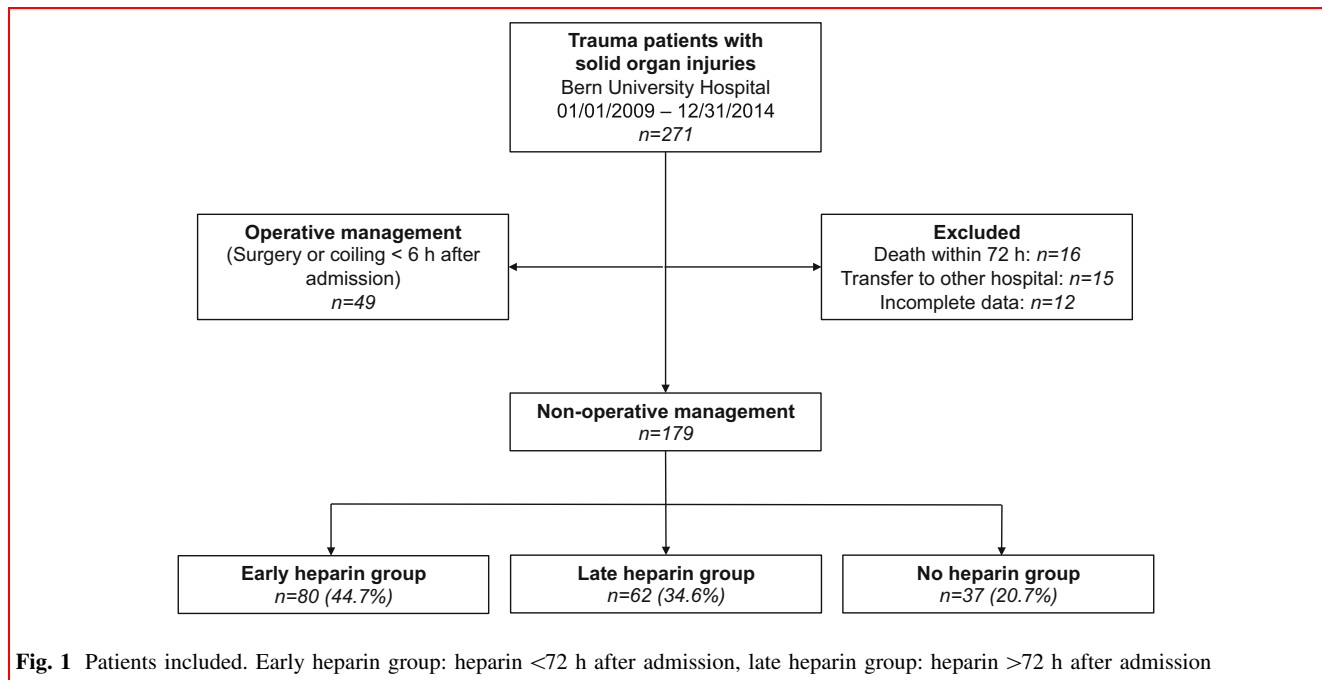
VTE included venous thrombosis and pulmonary embolism, diagnosed by Doppler ultrasound or high-resolution chest computed tomography (CT) scanning. No routine VTE screening was performed. Diagnostic imaging was performed only if clinical symptoms for VTE were present.

Abdominal CT scans were obtained on admission in all patients. Based on abdominal CT scans, SOI were classified according to the American Association for the Surgery of Trauma (AAST) Organ Injury Scale (OIS), and categorized into low-grade (OIS ≤ 3) and high-grade (OIS > 3) injuries [17, 18].

Thromboembolic prophylaxis with heparin

In patients selected for NOM, heparin (LMWH or LDUH) prophylaxis was started at the discretion of the attending surgeon within 24–72 h after hospital admission unless the patient had contraindications such as traumatic brain injury. The following heparin products were administered: Heparin (Liquemin[®], Calciparin[®]) 10,000 IU/24 h, Enoxaparin (Clexane[®]) 40 mg/24 h, or Nadroparin (Fraxiparin[®]).

Included patients were divided into three groups: thromboembolic prophylaxis with heparin ≤ 72 h after hospital

**Table 1** Baseline characteristics

	All patients (n = 179)	Early heparin (n = 80)	Late heparin (n = 62)	No heparin (n = 37)	p value [†]
Age (years) ^a	38.0 (27.9)	38.4 (29.4)	36.8 (30.7)	40.3 (21.5)	0.588 [‡]
Male gender	126 (70.4)	60 (75.0)	39 (62.9)	27 (73.0)	0.272
ISS ^a	21.0 (15.0)	17.0 (11.0)	29.0 (21.0)	18.0 (16.5)	<0.001 [‡]
AIS head ≥3	37 (20.7)	10 (12.5)	20 (32.3)	7 (18.9)	0.015
AIS chest ≥3	104 (58.1)	47 (58.8)	43 (69.4)	14 (37.8)	0.009
AIS abdomen ≥3	84 (46.9)	23 (28.8)	38 (61.3)	23 (62.2)	<0.001
AIS extremities ≥3	41 (22.9)	21 (26.3)	16 (25.8)	4 (10.8)	0.145
GCS ≤ 8	13 (7.3)	4 (5.0)	7 (11.3)	2 (5.4)	0.318
Severe pelvic/LE fracture	68 (38.0)	38 (47.8)	23 (37.1)	7 (18.9)	0.012
High-grade SOI	76 (42.5)	21 (26.3)	32 (51.6)	23 (62.2)	<0.001
Hollow viscus injury	2 (1.1)	0 (0.0)	1 (1.6)	1 (2.7)	0.390
Hypotension at admission	8 (4.5)	1 (1.3)	6 (9.7)	1 (2.7)	0.046
PRBC first 24 h	49 (27.4)	18 (22.5)	22 (35.5)	9 (24.3)	0.204
FFP in first 24 h	25 (14.0)	6 (7.6)	15 (24.2)	4 (10.8)	0.016
PLT first 24 h	10 (5.6)	2 (2.5)	7 (11.3)	1 (2.7)	0.054

Significant differences of variables are given in bold

Values are numbers (percentages) unless indicated otherwise

ISS Injury Severity Score, AIS Abbreviated Injury Scale, GCS Glasgow Coma Scale, LE lower extremity, SOI solid organ injury, PRBC packed red blood cells, FFP fresh frozen plasma

[†] Chi-square test. [‡] Kruskal–Wallis test

^a Values are medians (interquartile range)

admission ('early heparin group'), thromboembolic prophylaxis with heparin >72 h after hospital admission ('late heparin group'), and no prophylaxis with heparin during the hospital stay ('no heparin group').

Patient characteristics, injury characteristics, transfusion requirements within the first 24 h after admission, and outcome variables of the three groups were compared in univariate analysis. Factors affecting the timing of the

Table 2 Solid organ injuries and timing of heparin administration

	Total	Early heparin	Late heparin	No heparin	<i>p</i> value [†]
Splenic injury	69 (100)	32 (46.4)	20 (29.0)	17 (24.6)	0.375
High-grade injury	21 (100)	6 (28.6)	7 (33.3)	8 (38.1)	0.106
Risk factors for failed NOM ¹	16 (100)	5 (31.3)	5 (31.3)	6 (37.5)	0.292
Liver injury	97	39 (40.2)	37 (38.2)	21 (21.6)	0.406
High-grade injury	37 (100)	9 (24.3)	19 (51.4)	9 (24.3)	0.035
Risk factors for failed NOM ¹	30 (100)	6 (20.0)	17 (56.7)	7 (23.3)	0.015
Renal injury	58	25 (43.1)	20 (34.5)	13 (22.4)	0.916
High-grade injury	24 (100)	7 (29.2)	9 (37.5)	8 (33.3)	0.156
Risk factors for failed NOM ²	14 (100)	2 (14.3)	8 (57.1)	4 (28.6)	0.037

Significant differences of variables are given in bold

Values are numbers (percentages)

NOM non-operative management

[†] Chi-square test

¹ Contrast extravasation, pseudoaneurysm, massive hemoperitoneum, and vessel truncation

² Contrast extravasation, pseudoaneurysm, arteriovenous fistula, and vessel truncation

heparin prophylaxis, i.e., early versus late heparin administration, were analyzed with multivariate analysis.

Statistical analysis

Normality of distribution was assessed using histograms, skewness, and the Shapiro–Wilk test. In univariate analysis, categorical variables were compared using the Chi-square test and continuous variables using the Kruskal–Wallis test, as appropriate. Results were reported as numbers and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR), as appropriate. *p* values ≤ 0.05 were considered statistically significant.

The effect of clinically important predictor variables (sex, age, AIS head/chest/abdomen/extremities/external ≥ 3 , GCS, hypotension on admission, injured solid organ, and PRBC, FFP and PLT transfusion) on the timing of heparin prophylaxis (early vs. late) was analyzed in backward stepwise multivariate logistic regression analysis. The association of the clinically important predictor variables and early versus late heparin administration was analyzed in univariate analysis and entered in the regression model if the *p* value was < 0.1 . Results were reported as odds ratio (OR) and 95% confidence interval (CI). Interactions between the predictor variables were tested using separate logistic regression analyses. Multicollinearity was assessed using the variance inflation factor (VIF). A VIF < 5 was assumed to exclude significant collinearity. The goodness-of-fit of the regression model was assessed using Hosmer–Lemeshow statistics.

All statistical analyses were performed using SPSS statistics (Version 22, IBM Corporation, Armonk, NY).

Results

Included patients and baseline characteristics

A total of 271 adult trauma patients with blunt SOI were admitted during the 6-years study period. Of these, 179 patients fulfilled the inclusion criteria and were enrolled into the analysis. The ‘early heparin group’ comprised 80 patients (44.7%), the ‘late heparin group’ 62 patients (34.6%), and the ‘no heparin group’ 37 patients (20.7%) (Fig. 1).

Baseline characteristics of the included patients are shown in Table 1. Patients were predominately male (70.4%), had a median age of 38.0 years (IQR 27.9), and a median ISS of 21.0 (IQR 15.0). The median ISS of patients in the ‘late heparin group,’ was significantly higher compared to the median ISS in the ‘early heparin group’ and ‘no heparin group,’ respectively (29.0 vs. 17.0 vs. 18.0; $p < 0.001$). The percentage of patients receiving FFP within the first 24 h was significantly higher in the ‘late heparin group’ compared to the ‘early’ and ‘no heparin group’ (24.2 vs. 7.6 vs. 10.8%; $p = 0.016$). In the ‘early heparin group,’ severe pelvic and lower extremity fractures were significantly more frequent than in the ‘late heparin and ‘no heparin groups’ (47.8 vs. 37.1 vs. 18.9%; $p = 0.012$).

Solid organ injuries and timing of heparin administration

The median time of heparin administration was 57 h (IQR 71) after hospital admission.

Table 3 Characteristics of patients with failed non-operative management

Patient	Sex	Age (years)	Mechanism of injury	Solid organ injury ^a	Associated injuries	ISS	Intervention	Timing intervention (days after admission)	Start heparin (days after admission)	Risk factors
1	M	41	MVC	Spleen grade 3, liver grade 2	–	9	Splenectomy	17	–	AV-fistula
2	M	54	Fall more than 2 m	Spleen grade 3, liver grade 2	Ribs, scapula, spinefractures	22	Splenectomy	6	–	LAH
3	M	19	MVC	Spleen grade 4	Femur and clavicle fracture	25	Splenectomy	2	–	LAH
4	F	62	Fall less than 2 m	Spleen grade 4	Spine fractures with spinal cord contusion, rib fractures with hemothorax	18	Angioembolization	7	–	–
5	M	57	MVC	Liver grade 2, renal grade 2, pancreas grade 2	Complex cerebral and cervical injury, rib fractures with lung contusion, hemothorax bilateral	41	Splenectomy pancreatectomy	10	16	LAH
6	M	19	Fall more than 2 m	Spleen grade 4	–	16	Angioembolization	6	5	AV-fistula, LAH
7	F	40	MVC	Spleen grade 4	Cervical and thoracic spine fracture, multiple rib fractures with hemothorax, complex hip fracture	34	Splenectomy	1	–	Contrast extravasation

SOI solid organ injury, ISS Injury Severity Score, MVC motor vehicle collision, AV arterio-venous, LAH large amount of hemoperitoneum

^a According to the American Association for the Surgery of Trauma Organ Injury Scale

In patients receiving early heparin, 18.8% of the patients with splenic injuries, 30.8% of the patients with liver injuries, and 28.0% of the patients with renal injuries had high-grade injuries.

In patients with *splenic* injuries, the proportion of patients receiving early, late, or no heparin was not significantly different. This was also observed in the subgroups of patients with high-grade splenic injuries and patients with risk factors for failed NOM.

In patients with *liver* or *renal* injuries, the proportion of patients receiving early, late, or no heparin was not significantly different, whereas high-grade liver injuries and risk factors for NOM failure in patients with renal or liver injuries were significantly more frequent in the 'late heparin' than in the 'early' and 'no heparin group' (Table 2).

Outcomes

Failed NOM occurred only in patients with splenic injuries and was significantly more frequent in the 'no heparin group' than in the 'early' and 'late heparin group' (10.8, 3.2, and 1.3%, respectively; $p = 0.043$). The characteristics of patients with failed NOM are outlined in detail in Table 3.

The occurrence of VTE was not significantly different between the three heparin groups, although there was a strong trend toward more VTE in the 'no heparin group' compared to the 'early' and 'late heparin groups' (10.8, 4.8, and 1.3%, respectively; $p = 0.066$) (Table 4). The characteristics of patients with VTE are outlined in detail in Table 5.

In-hospital mortality was not significantly different between the three heparin groups. Only one patient from the 'late heparin group' died from severe traumatic brain injury (TBI) 11 days after admission.

Factors affecting the timing of heparin prophylaxis

Multivariate analysis for early versus late heparin prophylaxis included hypotension on admission, AIS (head, chest, abdomen, extremities, and external) ≥ 3 , GCS on admission, and PRBC, FFP, and PLT transfusion. AIS abdomen ≥ 3 (OR 4.550, CI 2.100–9.859, $p < 0.001$) and

AIS head ≥ 3 (OR 2.721, CI 1.026–7.212) were identified as independent predictors for late heparin prophylaxis. The regression model fits the data well (Hosmer–Lemeshow statistics: X^2 0.34, df 2, $p = 0.983$). No significant interaction or collinearity between the predictor variables of the regression model was detected. The VIF was < 4 in all predictor variables.

Discussion

This study evaluated the timing of LMWH or LDUH administration for prophylaxis of VTE in 179 trauma patients with SOI undergoing NOM. The overall incidence of failed NOM was low, i.e., 3.9%, which is in line with previous studies that reported failed NOM in 3.1–7.0% of trauma patients with SOI [13, 19–21]. However, in another study from our institution that analyzed the management of blunt splenic injuries, failed NOM was observed in 21% of patients with high-grade injuries [22]. Of the 80 patients that received heparin early, i.e., before 72 h after hospital admission, only one (1.3%) failed NOM and underwent angioembolization for a grade 4 splenic laceration at hospital day seven.

The proportion of trauma patients that received heparin early was 44.7% in the current study. This is the second highest rate of early prophylactic heparin administration reported so far. Rostas et al. [15] reported early LMWH administration (< 72 h) in 48.0% of included patients. However, this study population included less high-grade (OIS ≥ 3) liver and splenic injuries than the current study (12.8 vs. 39.2%). On the other hand, Eberle et al. [13], in their retrospective study including patients with SOI undergoing NOM, reported early LMWH administration in only 13.2% of included patients.

Not surprisingly, the median ISS and number of patients with severe TBI (AIS head ≥ 3) were significantly higher in patients with late compared to early heparin administration. The higher injury burden and potential TBI-related bleeding complications most likely delayed heparin administration in these patients. This is also supported by the multivariate

Table 4 Univariate analysis of outcome variables

	All patients ($n = 179$)	Early heparin ($n = 80$)	Late heparin ($n = 62$)	No heparin ($n = 37$)	p value [†]
Failed NOM	7 (3.9)	1 (1.3)	2 (3.2)	4 (10.8)	0.043
In-hospital mortality	1 (0.6)	0 (0.0)	1 (1.6)	0 (0.0)	0.390
Venous thromboembolism	8 (4.5)	1 (1.3)	3 (4.8)	4 (10.8)	0.066

Significant differences of variables are given in bold

Values are numbers (percentages)

NOM non-operative management

[†] Chi-square test

Table 5 Characteristics of patients with venous thromboembolism

Patient	Sex	Age (years)	Solid organ injury ^a	Associated injuries	Start heparin (days after admission)	VTE	Time of VTE diagnosis (days after admission)
1	M	31	Spleen grade 4	Traumatic brain injury, hemothorax, complex injuries of upper and lower extremities	4	PE	16
2	F	44	Liver grade 2	Hemothorax, rib fractures	–	PE	4
3	M	51	Spleen grade 3	Pelvic ring fracture, complex tibia fracture	5	PE	6
4	M	40	Liver grade 2, spleen grade 3	Pelvic ring fracture	–	DVT	50
5	M	54	Liver grade 1	Hemothorax, spine fracture, pelvic fracture	6	PE	52
6	M	19	Spleen grade 4	Clavicle fracture, femur fracture	2	PE	30
7	M	72	Liver grade 2, renal grade 2	Hemothorax	0	DVT	At admission
8	F	74	Liver grade 2	Traumatic brain injury, spine fracture, upper and lower extremity fractures	–	PE	30

VTE venous thromboembolism, PE pulmonary embolism, DVT deep venous thrombosis

^a According to the American Association for the Surgery of Trauma Organ Injury Scale

regression analysis that revealed AIS abdomen or head ≥ 3 as independent predictors for late heparin administration. The decision to avoid early heparin in these patients was at the discretion of the treating surgeon, which is in accordance with our institution's policy. However, whether higher ISS or severe TBI are contraindications for early prophylactic heparin needs to be addressed by future studies.

In contrast, early heparin administration was significantly more frequent in patients with pelvic and severe lower extremity fractures, which are well-known risk factors for VTE [7, 8]. Apparently, the high risk of VTE in this group of patients did outweigh the risk of bleeding complications, and therefore, prophylactic heparin was administered earlier.

Higher organ injury grades have been reported as risk factors for failed NOM in patients with splenic [23–25], hepatic [26, 27], and renal trauma [5, 28]. Interestingly, in patients with splenic injuries and risk factors for failed NOM, no significant difference between the 'early,' 'late,' and 'no heparin group' was found. However, in patients with liver or renal injuries and risk factors for failed NOM, late heparin administration was significantly more frequent than early heparin administration. It seems that rebleeding from liver or renal injuries was more feared than rebleeding from splenic injuries by the treating team. This is not supported by the literature, and hence, we believe that a more liberal use of heparin prophylaxis should be attempted in patients with liver or renal injuries.

In the present study, although statistically not significant, there was a strong trend toward less thromboembolic

complications in patients receiving early prophylactic heparin. Joseph et al. compared early (<48 h) versus intermediate (48–72 h) versus late (>72 h) VTE prophylaxis with LMWH in a propensity score-matched analysis of trauma patients with SOI undergoing NOM. In this study, the frequency of thromboembolic complications was also not significantly different between the three groups. Nevertheless, in the early prophylaxis group no thromboembolic event was reported, whereas the frequency of thromboembolic events was 3.4% in both, the intermediate and late VTE prophylaxis group [14]. The early administration of prophylactic heparin in trauma patients with SOI therefore may reduce the risk for thromboembolic complications, although this has not been proved so far, most likely due to underpowered studies. Further investigation of the effect of early heparin prophylaxis on VTE rates in patients with SOI in larger clinical trials is therefore warranted.

Finally, this study has some inherent limitations. Besides the usual limitations of retrospective studies, this single-center study may be underpowered to detect significant differences of infrequent events such as NOM failure, VTE, or in-hospital mortality. In addition, no standardized VTE screening was performed, and therefore, only clinically apparent VTE were assessed.

In conclusion, in patients with SOI undergoing NOM, heparin was administered early in a high percentage of patients and was not associated with an increased NOM failure rate or higher in-hospital mortality. Based on these results, the early administration of prophylactic heparin may be safe in patients with SOI undergoing NOM.

Compliance with ethical standards

Conflict of interest Tatsiana Khatsilouskaya, Tobias Haltmeier, Marionna Cathomas, Barbara Eberle, Daniel Candinas, and Beat Schnüriger have no conflicts of interest or financial ties to disclose.

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