

Original article

**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: Retrospective study including adult trauma patients with SOI (liver, spleen, kidney) undergoing non-operative management (NOM) 01/2009-12/2014. Three groups were distinguished: prophylactic heparin (low molecular weight heparin [LMWH] or low-dose unfractionated heparin [LDUH]) ≤ 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, 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.

Background

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 timepoint of heparin administration. Furthermore, only a limited number of patients that received heparin early (within 72 hours 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 to 72 hours 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 liver, splenic, and/or renal injuries that were admitted to the Bern University Hospital from 01/01/2009 to 12/31/2014. 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 hours 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 to 8 hours, and serial hemoglobin levels every 6 to 8 hours.

A surgical or radiological intervention \geq 6 hours after hospital admission was defined as failed NOM. Patients that died during the first 72 hours 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, 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], 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 hours 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/24h, Enoxaparin (Clexane®) 40mg/24h, or Nadroparin (Fraxiparin®).

Included patients were divided into three groups: thromboembolic prophylaxis with heparin ≤ 72 hours after hospital admission ('early heparin group'), thromboembolic prophylaxis with heparin > 72 hours 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 hours after admission, and outcome variables of the three groups were compared in univariate analysis. Factors affecting the timing of the 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 versus 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%). (*Figure 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 hours 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 hours (IQR 71) after hospital admission. 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 4*.

The occurrence of VTE was not significantly different between the three heparin groups, although there was a strong trend towards 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 3*). 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, 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 fit 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 to 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 hours 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 reported early LMWH administration (<72 hours) in 48.0% of included patients. However, this study population included less high-grade (OIS \geq 3) liver and splenic injuries than the current study (12.8% vs. 39.2%).¹⁵ On the other hand, Eberle et al, in their retrospective study including patients with SOI undergoing NOM, reported early LMWH administration in only 13.2% of included patients.¹³

Not surprisingly, the median ISS and number of patients with severe TBI (AIS head \geq 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 regression analysis that revealed AIS abdomen or head \geq 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 splenic²³⁻²⁵, 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 towards less thromboembolic complications in patients receiving early prophylactic heparin. Joseph et al compared early (< 48 hours) vs. intermediate (48 to 72 hours) vs. late (> 72 hours) 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.

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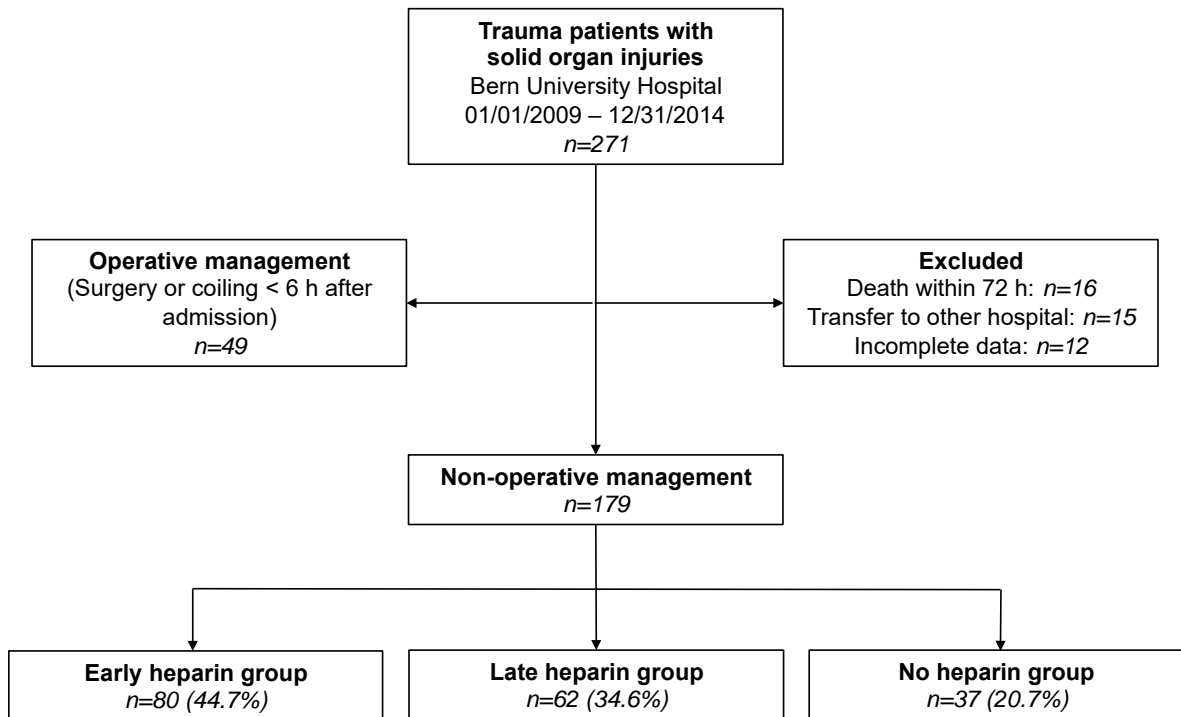
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Figures and Tables

Figure 1 Patients included



Early heparin group: heparin < 72 h after admission; Late heparin group: heparin > 72h after admission.

Table 1 Baseline characteristics

| | All patients (n=179) | Early heparin (n=80) | Late heparin (n=62) | No heparin (n=37) | p-value [†] |
|---------------------------|-------------------------|-------------------------|------------------------|----------------------|------------------------------|
| Age (years)* | 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* | 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 |

Values are numbers (percentages) unless indicated otherwise. *Values are medians (interquartile range).

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

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.

Table 2 Solid Organ Injuries and Timing of Heparin Administration

| | Total | Early heparin | Late heparin | No heparin | p-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 |

Values are numbers (percentages).

[†]Chi-square test.

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

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

NOM: non-operative management.

Table 3 Univariate analysis of outcome variables

| | All patients (<i>n</i> =179) | Early heparin (<i>n</i> =80) | Late heparin (<i>n</i> =62) | No heparin (<i>n</i> =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 thrombo-embolism | 8 (4.5) | 1 (1.3) | 3 (4.8) | 4 (10.8) | 0.066 |

Values are numbers (percentages)

[†]Chi-square test.

NOM: non-operative management.

Table 4 Characteristics of patients with failed non-operative management

| Patient | Sex | Age (years) | Mechanism of injury | Solid organ injury* | 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 hemato-pneumothorax | 18 | angioembolization | 7 | - | - |
| 5 | m | 57 | MVC | liver grade 2, renal grade 2, pancreas grade 2 | complex cerebral & cervical injury, rib fractures with lung contusion, hemato-pneumothorax 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 & thoracic spine fracture, multiple rib fractures with hemato-pneumothorax, complex hip fracture | 34 | splenectomy | 1 | - | Contrast extravasation |

*According to the American Association for the Surgery of Trauma Organ Injury Scale.

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

Table 5 Characteristics of patients with venous thromboembolism

| Patient | Sex | Age (years) | Solid organ injury | 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 & 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 |

*According to the American Association for the Surgery of Trauma Organ Injury Scale.
VTE: venous thromboembolism, PE: pulmonary embolism, DVT: deep venous thrombosis.