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Early thromboembolic prophylaxis in patients with blunt solid abdominal organ injuries undergoing nonoperative management: is it safe?

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Abstract

BACKGROUND: The aim of this study was to compare the safety of early (≤48 hours), intermediate (48 to 72 hours), and late (≥72 hours) venous thromboembolism prophylaxis in patients with blunt abdominal solid organ injury managed nonoperatively.

METHODS: We performed a 6-year (2006 to 2011) retrospective review of all trauma patients with blunt abdominal solid organ injuries. Patients were matched using propensity score matching in a 2:1:1 (early:intermediate:late) for age, gender, systolic blood pressure, Glasgow Coma Scale, Injury Severity Score, and type and grade of organs injured. Our primary outcome measures were: hemorrhage complications and need for intervention (operative intervention and/or angioembolization).

RESULTS: A total of 116 patients (58 early, 29 intermediate, and 29 late) were included. There were no differences in age ($P = .5$), Injury Severity Score ($P = .6$), type ($P = .1$), and grade of injury of the organ ($P = .6$) between the 3 groups. There were 67 liver (43.2%), 63 spleen (40.6%), 49 kidney (31.6%), and 24 multiple solid organ (15.4%) injuries. There was no difference in operative intervention ($P = .8$) and postprophylaxis blood transfusion ($P = .3$) between the 3 groups.

CONCLUSIONS: Early enoxaparin-based anticoagulation may be a safe option in trauma patients with blunt solid organ injury. This study showed no significant correlation between early anticoagulation and development of bleeding complications.

Blunt traumatic injury accounts for more than 80% of all trauma-related hospital admissions.[1,2] Abdominal solid organ (spleen, kidney, and liver) injuries are the most common injury pattern in patients with blunt trauma.[1–3] Nonoperative management (NOM) is the current standard of care for managing hemodynamically stable patients with blunt liver, kidney, or spleen injuries.[3–6] However, the management of these patients is challenging due to the inherent risks of developing

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venous thromboembolism (VTE) and associated failure of NOM.

The recently published guidelines by the American College of Chest Physicians recommend early initiation of VTE prophylaxis to reduce the incidence of thromboembolic complications in patients with multi-system trauma.[6] A national survey of all trauma surgeons and the guidelines from the Eastern Association for the Surgery of Trauma also support the practice of early VTE prophylaxis for solid organ injury.[4,5,7] However, these recommendations fail to define the optimal timing for initiation of VTE prophylaxis and also suggest the lack of evidence to support this practice in patients with blunt solid organ injury.

There have only been 2 studies assessing the timing of initiating VTE prophylaxis in patients with solid organ injury. One study recommended initiation of VTE prophylaxis within 72 hours of injury in patients with blunt liver, kidney, or spleen injury.[8] Another study advocated initiation of VTE prophylaxis within 48 hours in patients with isolated blunt spleen injury.[9] Nevertheless, there is paucity of data assessing the optimal timing of initiation of VTE prophylaxis in patients with blunt abdominal trauma. Additionally, the fear of failure of NOM and development of hemorrhagic complications play a detrimental role for early initiation of VTE prophylaxis.

The aim of this study was to compare the safety of early ($\leq$48 hours), intermediate (48 to 72 hours), and late ($\geq$72 hours) heparin-based VTE prophylaxis in NOM of blunt liver, kidney, and/or spleen trauma. We hypothesized that there is no difference in hemorrhagic complications and rate of intervention (operative and angioembolization) with early initiation of VTE prophylaxis compared with intermediate and late initiation of VTE prophylaxis.

Methods

After the approval from the Institutional Review Board of the University of Arizona, College of Medicine, we performed a 6-year (2006 to 2011) retrospective review of all trauma patients with blunt solid organ injuries who presented to our Level-1 trauma center. Patients with blunt solid organ injuries who underwent NOM and received VTE prophylaxis during their hospitalization were included. Patients transferred from other facilities and patients with isolated head injury (head Abbreviated Injury Severity Score (AIS) $\geq$3, and other body region AIS $<$ 3) were excluded.

We reviewed patient's electronic medical records and abstracted the following data points: demographic characteristics (age and gender), physiological parameters on presentation, which included systolic blood pressure (SBP), heart rate, and temperature, and Glasgow Coma Scale score; computed tomographic scan findings on presentation, laboratory parameters, which included prothrombin time, platelet count, and international normalized ratio (INR); and in-hospital complications, requirement of blood transfusion, hospital and intensive care unit length of stay, and in-hospital mortality. The injury severity score (ISS) and abbreviated injury scale (AIS) scores were obtained from the trauma registry. The pharmacy database was reviewed for the details of VTE prophylaxis in each patient including dose and time of administration of the drug.

The initial computed tomographic scans were reviewed by a single investigator for the type (liver, spleen, or kidney) of solid organ injured and the grade of injury. Each injured solid organ was graded based on the criteria published by the American Association for the Surgery of Trauma.[10]

All patients received VTE prophylaxis with low-molecular-weight heparin 30 mg subcutaneously every 12 hours. We then stratified patients into 3 groups based on the time of initiation of VTE prophylaxis: early ($\leq$48 hours), intermediate (48 to 72 hours), and late ($\geq$72 hours). Propensity scoring matched patients in 3 groups in a 2:1:1 (early:intermediate:late) based on age, gender, SBP, Glasgow Coma Scale, ISS, organs injured, and grade of injury of the organ.

Propensity matching is analogous to the process of randomization of a clinical trial that is commonly used in an observational study. A propensity score denotes the conditional probability of an individual to receive a certain treatment (timing of VTE prophylaxis). A propensity score was generated for each patient based on confounding factors using a logistic regression model. The patients in the 3 groups were then matched based on their propensity scores within .00001 of the estimated score. The accuracy of the model was quantified using the area under the receiver operator characteristic curve.

Our primary outcome measures were: hemorrhagic complications and requirement of an intervention. The secondary outcome measures were: thromboembolic complications and in-hospital mortality. Hemorrhagic complications were assessed based on postprophylaxis blood product requirement. We defined requirement of an intervention as operative intervention or angioembolization. Failure of NOM was defined as requirement of operative intervention. Thromboembolic complications were defined as deep venous thrombosis or pulmonary embolism.

Data are reported as mean $\pm$ standard deviation for continuous descriptive variables, median (range) for ordinal descriptive variables, and as proportions for categorical variables. We performed Mann-Whitney U and Student t tests to explore for differences in the 3 groups (early, intermediate, and late thromboembolic prophylaxis) for continuous variables. We used chi-square test to identify differences in outcomes between the 3 groups for categorical variables. For our study, we considered P value less than .05 as statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS version 20; SPSS, Inc., Chicago, IL, USA).

Results

A total of 852 patients with blunt solid organ injuries that were managed nonoperatively were reviewed. Of which, 274 patients met inclusion criteria. After matching,

Table 1 Demographics

Variables	Early (n = 58)	Intermediate (n = 29)	Late (n = 29)	P value
Demographics				
Age, years, mean ± SD	39.5 ± 18.2	44.3 ± 21.4	45.1 ± 22.9	.3
Male, %	67.2	69	72.4	.7
Physiologic parameters				
ED GCS, median (IQR)	15 (14–15)	15 (14–15)	14 (14–15)	.9
ED systolic BP, mean ± SD	133.6 ± 27.5	130.7 ± 24.7	134.3 ± 25.8	.7
ED heart rate, mean ± SD	94.2 ± 16.8	96.4 ± 20.1	98.2 ± 17.8	.8
ED temperature, mean ± SD	36.4 ± .8	36 ± .6	35.8 ± .9	.9
Laboratory parameters				
PT, %, mean ± SD	31.2	29.7	32.5	.2
Platelet count, mean ± SD	279 ± 59.6	269.4 ± 78.8	282.5 ± 89.4	.6
INR, mean ± SD	1.1 ± .4	1.2 ± .8	1.1 ± .3	.5
INR > 1.5, %	3.4	6.9	10.3	.2
Injury parameters				
ISS, median (IQR)	17 (12–19)	17 (14–24)	17 (13–26)	.8
ISS ≥ 25, %	13.8	20.7	13.7	.7
Abdominal AIS, median (IQR)	2 (2–3)	2 (2–3)	2 (2–4)	.8
Abdominal AIS > 3, %	37.9	20.7	24.1	.3

AIS = abbreviated injury scale; BP = systolic blood pressure; ED = emergency department; GCS = Glasgow coma scale; INR = international normalized ratio; ISS = injury severity score; IQR = interquartile range; PT = prothrombin time; SD = standard deviation.

a total of 116 patients (58 early, 29 intermediate, and 29 late) were included in the analysis. The mean age was 42.2 ± 20.3 years, 66.4% were males, mean SBP was 130.5 ± 26.5 mm Hg, and median ISS was 17 (12 to 22). There were no differences in age (P = .5), SBP (P = .8), INR on presentation (P = .5), and injury severity (P = .6) between the 3 groups. Table 1 demonstrates the demographics of the study population.

Of the study population, 43.2% patients (n = 67) had liver injury, 40.6% (n = 63) had splenic injury, 31.6% (n = 49) had kidney injury, and 15.4% (n = 24) had multiple solid organ injuries. There was no difference in type (P = .1) and grade of injury of solid organ (P = .6) between patients receiving early, intermediate, and late VTE prophylaxis. Table 2 demonstrates the type and grade of solid organs injured between the 3 groups.

Table 3 highlights the laboratory parameters and postprophylaxis blood transfusion requirement between the 3 groups. There was no difference in the INR (P = .4) and postprophylaxis blood transfusion requirement (P = .3) between the 3 groups.

Three patients (2.6%) underwent angioembolization. There was no difference in the rate of angioembolization (P = .8) between the 3 groups. No patient required an operative intervention. The overall thromboembolic complication rate was 1.7% (n = 2). There was no difference in the incidence of thromboembolic complications between the 3 groups. Table 4 highlights the operative intervention and outcomes between the 3 groups.

Comments

The fears of development of hemorrhagic complications and failure of NOM limit the early initiation of thromboembolic prophylaxis in patients with blunt solid organ injury.[3,8,9] This study demonstrates that early enoxaparin-based anticoagulation may be safe in patients with blunt solid organ injury. In our matched cohort of patients, we found no difference in development of hemorrhagic complications and the rate of intervention between patients receiving early, intermediate, or late VTE

Table 2 Details of solid organ injured

Organ injured	Early (n = 58)	Intermediate (n = 29)	Late (n = 29)	P value
Spleen, %	41.4	37.9	45.2	.6
Grade ≥3, %	15.5	20.6	24.1	.1
Kidney, %	31	27.6	27.6	.5
Grade ≥3, %	13.8	13.8	17.2	.8
Liver, %	25.9	27.6	24.1	.8
Grade ≥3, %	12	13.8	17.2	.6
Combined, %	18.9	20.7	17.2	.7

Table 3 Postprophylaxis laboratory parameters and blood transfusion

Variables	Early (n = 58)	Intermediate (n = 29)	Late (n = 29)	P value
INR, mean ± SD	1.1 ± .3	1.2 ± .2	1 ± .4	.5
PT, mean ± SD	15.7 ± 2.2	16 ± 3.6	15.1 ± 3.1	.8
Platelet count ($\times 10^3$), mean ± SD	279 ± 59.6	269.4 ± 78.8	282.5 ± 89.4	.6
Blood products received, n (%)	2 (3.4)	0	0	.3
PRBC units, mean ± SD	2.1 ± 1.5	0	0	.8

INR = international normalized ratio; PRBC = packed red blood cells; PT = prothrombin time; SD = standard deviation.

prophylaxis. There was a trend toward higher incidence of thromboembolic complications in patients with late initiation of VTE prophylaxis. Our study provides evidence-based data to better define the optimal timing (within 24 hours) for initiation of VTE prophylaxis in patients with blunt solid organ injury.

The guidelines developed by the American College of Chest Physicians and the Eastern Association for the Surgery of Trauma both highlight the lack of evidence to define the timing for initiation of VTE prophylaxis.[4–6] Only 2 studies have assessed the timing of initiating VTE prophylaxis in this cohort of patients.[8,9] Eberle et al,[8] in a retrospective review of patients with blunt spleen, kidney, and liver injury, demonstrated that initiation of VTE prophylaxis within 72 hours of hospitalization was safe. Similarly, Alejandro et al,[9] in a study of patients with isolated blunt splenic injury, demonstrated that VTE prophylaxis within 48 hours of hospital admission was safe. However, both these studies had a heterogeneous unmatched patient population, and there was variability in the type of VTE prophylaxis the patients received. Additionally, Alejandro et al only assessed patients with isolated splenic injury. In our matched cohort of patients with blunt liver, spleen, or kidney injuries, we found that early (≤48 hours) VTE prophylaxis was safe compared with intermediate or late VTE prophylaxis. Our study adds to the literature which supports the early use of VTE prophylaxis in blunt solid organ injury patients.

In our study, there was no difference in rate of intervention between early, intermediate, and late VTE prophylaxis groups. Only 3 patients required an intervention (angioembolization), and need for intervention was seen in all 3 groups. No patient failed NOM. All these three patients had a high-grade (≥3) splenic injury. Eberle et al[8] also demonstrated no difference in rate of operative intervention between early (within 72 hours) versus late (>72 hours) VTE prophylaxis with highest rate of failure in patients with high-grade splenic injury. Similarly, Aljandro et al[9] also demonstrated no difference in intervention rate with early (within 48 hours) and late (>48 hours) VTE prophylaxis. However, the overall rate of failure of NOM in both these studies was double the rate of our study (Eberle et al, 5.5%; Aljandro et al, 5.2%). The inclusion of patients with concomitant head and/or spinal cord injury along with blunt solid organ injury can explain the higher failure rates of NOM in these studies. In our study, we excluded patients with isolated head and/or spine injury as these are known predictors for failure of NOM. Additionally, we wanted to make our study population uniform to assess the true impact of early VTE prophylaxis in patients with blunt solid organ injury.

The development of bleeding complications is another major concern for initiating early VTE prophylaxis in blunt solid organ injury patients, which may require blood product transfusion. In our study, there was no difference in the requirement of postprophylaxis blood products in patients with early, intermediate, and late VTE prophylaxis. Contrastingly, Eberle et al[8] demonstrated higher blood product requirement in patients within the late VTE prophylaxis groups. These counter intuitive results can be explained based on high proportion of patients in the late VTE group with pelvic and/or lower extremity fractures requiring blood transfusion.

Table 4 Outcomes

Variables	Early (n = 58)	Intermediate (n = 29)	Late (n = 29)	P value
Interventions				
Embolization, n (%)	1 (1.7)	1 (3.4)	1 (3.4)	.8
Operative intervention, %	0	0	0	—
Complications				
Thromboembolism, n (%)	0	1 (3.4)	1 (3.4)	.3
Length of stay				
Hospital LOS, mean ± SD	3.9 ± 2.9	4.1 ± 3.6	4.8 ± 4.1	.2
ICU LOS, mean ± SD	2.1 ± 1.9	2.5 ± 2.1	2.4 ± 2.3	.4
Mortality, %	0	0	0	—

ICU = intensive care unit; LOS = length of stay; SD = standard deviation.

In is known that the overall incidence of thromboembolic complications after blunt solid organ injury is low.[3,8] Eberle et al,[8] in a retrospective review of patients with blunt solid organ injury, demonstrated a 1.2% rate in development of thromboembolic complication. Similarly, Norwood et al, in a study of patients blunt injury and high risk for development of thromboembolic complications, only 2 patients (1%) developed complications.[3] In our matched cohort of patients, the rate for thromboembolic complications was 1.7% ($n = 2$), which is comparable with other studies. Given this low incidence of thromboembolic complications in this cohort of patients, we determined our primary outcome measure as development of hemorrhagic complications and not development of thromboembolic complications. We found no difference in the rate of development of hemorrhagic complication; however, there was an increase toward the incidence of thromboembolic complications with delay in initiation of VTE prophylaxis. The 2 patients (1 intermediate and 1 late) who developed thromboembolic complications (both developed DVT) had high-grade splenic injury. The absence of thromboembolic complication in the early VTE group highlights the benefits of early VTE prophylaxis, which is supported by several studies in the literature.

We understand that our study has a small sample size to address the question of optimal timing for initiation of VTE prophylaxis in patients with blunt solid organ injury. However; our study includes a homogenous patient population which is propensity score matched to control for all the confounding factors, which may be associated with increased risk of both hemorrhagic and thromboembolic complications. Additionally, the rate of hemorrhagic and thromboembolic complications in our study was comparable with that of others studies published in the literature. Given the paucity of data and lack of definite guidelines, our study provides evidence-based literature to help clinicians better define the timing for initiation of VTE prophylaxis in patients with isolated blunt solid organ injury.

Our study comes with the inherent limitation of a retrospective study design with a small sample size. Second, although we matched patients for all the confounding factors, we were unable to control for certain factors. Third, we did not have a strict established protocol for initiation of VTE prophylaxis during the study period and did not assess the role of mechanical prophylaxis in our study population. Fourth, we did not perform routine screening of patients for development of thromboembolic complications. Despite these limitations, our study in a matched cohort of patients adds to the literature supporting the early use of VTE prophylaxis in patients with blunt liver, spleen, and kidney injury.

Conclusions

Early enoxaparin-based anticoagulation may be a safe option in trauma patients with blunt solid organ injury. This study showed no significant correlation between early anticoagulation and development of bleeding complications. Future prospective studies are required to define the impact of early VTE prophylaxis in the trauma patients.

References

1. Hoyt DB, Coimbra R, Engelhardt S et al. Trauma-specific Injuries; Essential Surgical Practice. 4th ed. 2002;1:17.
2. Isenhour JL, Marx J. Advances in abdominal trauma. Emerg Med Clin North Am 2007;25:713–33.
3. Norwood SH, McAuley CE, Berne JD, et al. A potentially expanded role for enoxaparin in preventing venous thromboembolism in high risk blunt trauma patients. J Am Coll Surg 2001;192:161–7.
4. Stassen NA, Bhullar I, Cheng JD, et al. Selective non-operative management of blunt splenic injury: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg 2012;73:S294–300.
5. Stassen NA, Bhullar I, Cheng JD, et al. Non-operative management of blunt hepatic injury: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg 2012;73:S288–93.
6. Could MK, Garcia DA, Wren SM, et al. Prevention of VTE in Nonorthopedic surgical patients. Chest 2012;141(2 Suppl):e227S–77S.
7. Zarzaur BL, Kozar RA, Fabian TC, et al. A survey of American Association for the Surgery of Trauma member practices in the management of blunt splenic injury. J Trauma 2011;70:1026–31.
8. Eberle BM, Schnüriger B, Inaba K, et al. Thromboembolic prophylaxis with low-molecular-weight heparin in patients with blunt solid abdominal organ injuries undergoing non-operative management: current practice and outcomes. J Trauma Acute Care Surg Jan 2011;70:141–7.
9. Alejandro KV, Acosta JA, Rodriguez PA. Bleeding manifestations after early use of low-molecular-weight heparins in blunt splenic injuries. Am Surg 2003;69:1006–9.
10. Moore EE, Cogbill TH, Jurkovich GJ, et al. Organ injury scaling (1994 revision). J Trauma 1995;38:323–4.