# Very early initiation of chemical venous thromboembolism prophylaxis after blunt solid organ injury is safe

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**Background:** The optimal timing of initiating low–molecular weight heparin (LMWH) in patients who have undergone nonoperative management (NOM) of blunt solid organ injuries (SOIs) remains controversial. We describe the safety of early initiation of chemical venous thromboembolism (VTE) prophylaxis among patients undergoing NOM of blunt SOIs.

**Methods:** We retrospectively studied severely injured adults who sustained blunt SOI without significant intracranial hemorrhage and underwent an initial NOM at a Canadian lead trauma hospital between 2010 and 2014. Safety was assessed based on failure of NOM, defined as the need for operative intervention, in patients who received early (< 48 h) or late LMWH (≥ 48 h, or early discharge [< 72 h] without LMWH).

**Results:** We included 162 patients in our analysis. Most were men (69%), and the average age was 42 ± 18 years. The median injury severity score was 17, and splenic injuries were most common (97 [60%], median grade 2), followed by liver (57 [35%], median grade 2) and kidney injuries (31 [19%], median grade 1). Combined injuries were present in 14% of patients. A total of 78 (48%) patients received early LMWH, while 84 (52%) received late LMWH. The groups differed only in percent of high-grade splenic injury (14% v. 32%). Overall 2% of patients failed NOM, none after receiving LMWH. Semielective angiography was performed in 23 (14%) patients. The overall rate of confirmed VTE on imaging was 1.9%.

**Conclusion:** Early initiation of medical thromboembolic prophylaxis appears safe in select patients with isolated SOI following blunt trauma. A prospective multicentre study is warranted.

**Contexte :** Le moment optimal pour commencer le traitement à l'héparine de bas poids moléculaire (HBPM) chez les patients ayant subi un traumatisme fermé à un organe plein (TFOP) avec prise en charge non chirurgicale (PCNC) demeure un sujet controversé. Nous décrivons l'innocuité d'une initiation hâtive de la chimioprophylaxie de la thromboembolie veineuse (TEV) chez les patients dont le TFOP est pris en charge de façon non chirurgicale.

**Méthodes :** Nous avons étudié rétrospectivement les cas d'adultes gravement blessés ayant subi un TFOP sans hémorragie intracrânienne importante pris en charge de façon non chirurgicale dans un hôpital canadien de premier plan spécialisé en traumatologie entre 2010 et 2014. L'innocuité a été évaluée en fonction du taux d'échec de la PCNC, défini comme la nécessité de recourir à une intervention chirurgicale, chez des patients qui ont reçu de l'HBPM plus tôt (< 48 h) ou plus tard (≥ 48 h, ou qui ont reçu un congé précoce [< 72 h]).

**Résultats :** Pour notre analyse, nous avons retenu 162 patients, en majorité des hommes (69 %), dont l'âge moyen était de 42 ± 18 ans. L'indice médian de gravité de la blessure était de 17; les lésions à la rate étaient les plus fréquentes (97 [60 %], stade médian 2), suivies des lésions du foie (57 [35 %], stade médian 2) et des lésions du rein (31 [19 %], stade médian 1). Il y avait présence de lésions combinées chez 14 % des patients. Au total, 78 patients (48 %) ont reçu de l'HBPM plus tôt, comparativement à 84 (52 %) qui en ont reçu plus tard. Seul le pourcentage de lésions spléniques graves était différent chez les 2 groupes (14 % comparativement à 32 %). La PCNC a échoué chez 2 % des patients, et chez aucun patient après l'administration d'HBPM. Une angiographie semi-urgente a été réalisée chez 23 patients (14 %). Le taux global de TEV confirmée par imagerie était de 1,9 %.

**Conclusion :** L'initiation hâtive de la prophylaxie de la TEV semble être sans danger chez certains patients ayant subi un traumatisme fermé et isolé à un organe plein. Il y a lieu de réaliser une étude multicentrique prospective.

Trauma patients are at high risk of venous thromboembolism (VTE). Without any prophylaxis, more than 50% may experience deep vein thrombosis (DVT), which substantially increases the risk of pulmonary embolism (PE).[1,2] In trauma patients who survive 24 hours, PE is the third leading cause of death.[3] Even with chemical prophylaxis, DVT can be detected in 15% of patients when screened with duplex ultrasonography.[4]

Trauma patients can be one of the most difficult populations in which to initiate chemical prophylaxis. Typically an initial coagulopathic state transitions to a hypercoaguable state within 48 hours of injury.[5] Both the American College of Chest Physicians[6] and the Eastern Association for the Surgery of Trauma[7] have released guidelines regarding chemical VTE prophylaxis following trauma and recommend early chemical VTE prophylaxis. While this is an achievable goal in many patients, those with solid organ injuries (SOIs) represent a unique challenge, especially in the presence of head injury. Nonoperative management (NOM) of blunt SOIs is becoming more common, and the safety of early initiation of chemical VTE prophylaxis in this unique population remains unclear.[8]

The goal of our study was to determine the rate of failure of NOM with early initiation of chemical VTE prophylaxis in patients with isolated blunt SOIs who undergo an initial trial of NOM.

## Methods

The London Health Sciences Centre (LHSC) is a lead trauma centre in Southwestern Ontario, Canada, with an approximate catchment of 1.5 million people. The LHSC maintains a trauma database for all trauma activations or patients with an injury severity score (ISS) greater than 12. The information in the locally maintained trauma database is collected prospectively, with less than 1% of data missing. The LHSC admits approximately 360 patients per year with an ISS greater than 12.

We queried the database to identify all adult patients (≥ 18 yr) with blunt splenic, liver, or kidney injuries, or any combination thereof, treated at the LHSC between April 2010 and February 2014. We excluded patients with a significant head injury (Maximum Abbreviated Injury Score [MAIS] of the head > 2), patients with penetrating trauma, those who died within 24 hours of presentation and those who were injured more than 24 hours before presentation to hospital.

We defined operative management based on the intial treatment plan from reviewing the trauma team leader and general surgery documentation. We considered patients to have undergone NOM if they did not receive an operation as part of their initial treatment plans or if they underwent angiography urgently or electively for embolization. The use of NOM for blunt SOI at LHSC is not based on a protocol. Patients with a splenic injury undergo follow-up computed tomography (CT) at 48 hours to assess for pseudoaneuryms. When splenic pesudoaneurysms are found, patients receive elective embolization before discharge. A similar strategy exists for high-grade liver injuries. Based on our prior work,[9] routine repeat imaging is performed in all patients with liver injuries classified as grade 3 or greater to assess for the presence of pseudoaneurysm. Repeat imaging for low-grade liver injuries and all grades of kidney injuries are left to the discretion of the attending trauma physician. Venous thromboembolism prophylaxis includes low–molecular weight heparin (LMWH; dalteparin 5000 IU subcutaneous injections daily), sequential compression devices and thromboembolism-deterrent stockings at the discretion of the attending trauma physician. There is no routine screening for DVT or PE.

We divided the study cohort into 2 groups: patients who received LMWH within 48 hours of admission (early) and patients who received LMWH more than 48 hours after admission or who did not receive LWMH but were discharged after less than 72 hours (late).

We reviewed the electronic and paper medical records of all included patients. The primary outcome of interest was failure of NOM, defined as an abdominal operation while in hospital after an initial trial of NOM based on a review of documentation from the trauma and general surgery services. Elective (> 24 h) or urgent (< 24 h) angiography was not defined as failure of NOM, but was recorded. Timing of failure of the intervention in relation to initiation of chemical VTE prophylaxis was also recorded. Secondary outcomes included the need for blood transfusion. Additional data collected included demographic characteristics, ISS, MAIS, Glasgow Coma Scale (GCS) score, grade of solid organ injury, hemodynamics on arrival to the trauma centre and length of stay in hospital. Grade of injury was classified according to the American Association for the Surgery of Trauma. Injuries were classified based on a review of CT findings as dictated by the attending board-certified radiologist, and those that were grade 3 and higher were considered to be high-grade. Deep vein thrombosis and PE were recorded if they were identified in the final dictated report for the ultrasound and CT pulmonary angiogram, respectively.

Approval for this study was obtained from the Research Ethics Board at Western University (REB Number 106030).

### *Statistical analysis*

We analyzed the data using SPSS software version 22. Data are presented as means with standard deviations for normally distributed continuous variables, medians with interquartile ranges (IQR) for non-normally distributed continuous variables, and frequencies with percentages for categorical variables. We compared the continuous

variables using the Student *t* test or the Mann–Whitney *U* test and categorical variables using the Pearson $\chi^2$ or Fisher exact test, as appropriate. We considered results to be significant at $p < 0.05$.

## Results

From April 2010 to March 2014 there were 287 patients with splenic, liver, kidney injuries or a combination thereof admitted to the LHSC trauma centres. Of the 287 patients there were 44 patients younger than 18 years, 20 who presented to hospital more than 24 hours after trauma, 18 who had a component of penetrating trauma and 4 who died within 24 hours. None of the patients who died within 24 hours received LMWH. These patients were excluded from our analysis, leaving 201 adults with blunt splenic, liver and/or kidney injuries available for analysis. Of these 201 patients, 24 (12%) were initially managed with operative exploration; therefore our final cohort included 162 patients. Seventy-eight patients received LMWH within 48 hours (early group). The mean time to initiation of LMWH in this group was 23 ± 12 hours. The late LMWH group comprised 84 patients. Fifteen patients had a length of stay longer than 72 hours and did not receive LMWH at the discretion of the attending trauma physician; they were excluded from further analysis. The demographic characteristics of the overall population and univariate comparisons between the early and late LMWH groups can be found in Table 1. Overall, the population was moderately injured with a mean ISS of 19 ± 9. The average patient age was 42 ± 18 years, and 69% were men. Baseline characteristics were similar between the 2 groups. The only significant difference was a higher proportion of high-grade splenic injuries in the late LMWH group (14% v. 32%, $p = 0.007$).

Of the 162 patients with an initial management plan of nonoperative management, 17 (10.5%) were managed with urgent angiography for active extravasation; NOM failed in 1 of these patients, who required operative intervention (Table 2). Two additional patients required operative intervention, without an attempt of angioembolization, giving a failure rate of 1.9%. No patient failed NOM after receiving LMWH. Semiurgent angiography was performed in 23 (15.9%) patients for pseudoaneurysms. The majority (136 [84%]) of patients required no angiographic or operative intervention. While there was no difference in the need for transfusion between groups (33% v. 30%, $p = 0.74$), more patients in the early LMWH group required transfusion after initiation of LMWH (21% v. 5%, $p = 0.005$). Further, among patients who required a blood transfusion, a median of 4.5 units of blood (IQR 2–8) were required during the hospital stay in the early LMWH group compared with a median of 2 units (IQR 2–4) in the late LMWH group ($p = 0.08$).

Three patients were confirmed to have VTE on imaging: 1 with a DVT and 2 with a PE, giving an overall VTE rate of 1.9%. All patients with a symptomatic VTE

**Table 1. Demographic characteristics of patients with blunt SOI undergoing NOM**

| Characteristic | Group; mean ± SD* Total, *n* = 162 | Early, *n* = 78 | Late, *n* = 84 | *p* value |
|---|---|---|---|---|
| Age, yr | 42 ± 18 | 43 ± 19 | 41 ± 18 | 0.56 |
| Male sex, no. (%) | 111 (69) | 52 (67) | 59 (70) | 0.63 |
| ISS | 19 ± 9 | 21 ± 9 | 17 ± 9 | 0.016 |
| SBP, mm Hg | 128 ± 22 | 130 ± 24 | 127 ± 19 | 0.38 |
| Heart rate, bpm | 91 ± 18 | 93 ± 16 | 89 ± 19 | 0.13 |
| Temperature, °C | 36.6 ± 0.8 | 36.4 ± 0.8 | 36.6 ± 0.9 | 0.21 |
| Organ injury | | | | |
| Spleen, no. (%) | 97 (60) | 42 (54) | 55 (66) | 0.13 |
| Median grade (IQR) | 2 (1–3) | 2 (1–3) | 2 (2–4) | 0.002 |
| High grade, no. (%) | 38 (24) | 11 (14) | 27 (32) | 0.007 |
| Liver, no. (%) | 57 (35) | 26 (33) | 31 (37) | 0.63 |
| Median grade (IQR) | 2 (1–3) | 2 (1–3) | 2 (1–3) | 0.93 |
| High grade, no. (%) | 19 (12) | 9 (12) | 10 (12) | 0.94 |
| Kidney, no. (%) | 31 (19) | 18 (23) | 13 (16) | 0.22 |
| Median grade (IQR) | 1 (1–2) | 1 (1–2) | 1 (1–2) | 0.95 |
| High grade, no. (%) | 7 (4) | 2 (3) | 5 (6) | 0.45 |
| Combined injuries, no. (%) | 23 (14) | 11 (14) | 12 (14) | 0.97 |

bpm = beats per minute; IQR = interquartile range; ISS = injury severity score; NOM = nonoperative management; SBP = systolic blood pressure; SD = standard deviation; SOI = solid organ injury.

*Unless indicated otherwise.

**Table 2. Characteristics of NOM and failure of NOM and transfusions**

| Characteristic | Group; no. (%)* Total, *n* = 162 | Early, *n* = 78 | Late, *n* = 84 | *p* value |
|---|---|---|---|---|
| No intervention | 145 (90) | 73 (94) | 72 (86) | 0.13 |
| Urgent embolization | 17 (10) | 5 (6) | 12 (14) | 0.13 |
| Elective embolization | 23 (14) | 6 (8) | 17 (20) | 0.03 |
| After LMWH | 8 (35) | 6 (100) | 2 (12) | 0.003 |
| Failure of NOM | 3 (4) | 2 (3) | 1 (1) | 0.60 |
| After LMWH | 0 | 0 | 0 | — |
| Transfusion | 51 (32) | 26 (33) | 25 (30) | 0.74 |
| pRBC < 24 h, median (IQR)† | 2 (0–4) | 2 (0–6) | 2 (0.5–3.5) | 0.56 |
| Total pRBC, median (IQR)† | 3 (2–6) | 4.5 (2–8.25) | 2 (2–4) | 0.08 |
| After LMWH | 21 (13) | 16 (21) | 5 (5) | 0.005 |
| LOS, median (IQR) | 5 (3–8) | 7 (4–9) | 4 (3–7) | 0.001 |
| SCU, median (IQR) | 3 (1–5) | 3 (1–6) | 3 (2–4) | 0.07 |
| VTE | | | | 0.10 |
| PE, no. | 2 | 2 | 0 | 0.20 |
| DVT, no. | 1 | 1 | 0 | 0.48 |

DVT = deep vein thrombosis; IQR = interquartile range; LMWH = low–molecular weight heparin; LOS = length of stay; NOM = nonoperative management; pRBC = packed red blood cells; SCU = special care unit; VTE = venous thromboembolism; PE = pulmonary embolism.

*Unless indicated otherwise.

†Median number of blood products in patients who received a transfusion.

received LMWH less than 48 hours after admission and went on to receive appropriate therapeutic anticoagulation. Only 1 patient in this cohort died; this patient was infected with *Clostridium difficile* after an extended stay in the intensive care unit.

## Discussion

The challenge of chemical VTE prophylaxis lies in the balance of hemorrhage and hypercoagulability unique to traumatically injured patients. This is particularly true in patients managed nonoperatively where supportive, largely noninvasive treatments are favoured instead of definitive surgical management. Fears of early hemorrhagic complications have historically limited early initiation of chemical VTE prophylaxis. More recently, however, limited evidence has come out supporting the safety of early initiation of chemical VTE prophylaxis.[10–12] Our study adds further support for the safety of early (< 48 h) initiation of LMWH for VTE prophylaxis in patients with blunt SOIs and no significant intracranial pathology. The overall rate of failure of NOM was very low in this study, and suggests we are correctly identifying appropriate patients for a trial of NOM. Nonetheless, we found no difference in the failure rate of NOM between patients who received early or late LMWH. The incidence of VTE was similar to that in other cohorts; however, all instances of VTE in this study were in patients receiving early rather than late chemical VTE prophylaxis.[10–12]

Current guidelines highlight a lack of evidence for or against early initiation of chemical VTE prophylaxis in patients undergoing NOM of blunt SOIs and have in particular stressed the unique challenge of managing these patients.[8] A lack of evidence precluded recommendations on this specific patient population particularly regarding the timing of chemical VTE prophylaxis by the Eastern Association for the Surgery of Trauma.[13,14] Four recent retrospective studies have attempted to address this problem. Similar to our work, a Canadian multicentre study reported in 2009 reviewed 72 patients with blunt hepatic injuries and found that those receiving delayed chemical VTE prophylaxis were more likely to have a high-grade injury.[15] In this study, it was demonstrated that a greater number of blood transfusions were given to the delayed group, with 44% of patients requiring transfusion compared with 26% in the early group. The authors concluded that early chemical VTE prophylaxis is safe, and they reported standardizing early administration at the study institution.[15] In 2002, Alejandro and colleagues[10] reported on 114 patients with blunt splenic injury. Failure rates of nonoperative management (5%) were no different between early and late chemical VTE prophylaxis and were similar to our reported rates. Eberle and colleagues[11] reviewed the cases of 312 patients undergoing NOM of SOIs and did not exclude those with head injuries. More than two-thirds of the patients did not receive chemical VTE prophylaxis, leaving a sample size of 111 patients. Compared with our population, their patients had higher ISS scores and a larger number of high-grade injuries. Again, failure rates of 5% were reported, particularly in those patients with high-grade spleen injuries; however, there was no difference between early and late groups. Joseph and colleagues[12] performed propensity score matching on 116 patients receiving early, intermediate and late chemical VTE prophylaxis and who did not have significant head injuries. By matching for confounding factors such as age, sex, systolic blood pressure, GCS score, ISS and grade of organ injury, bias was certainly limited. No patient failed NOM and only 3 patients required embolization, which is substantially fewer patients than in our cohort. This difference can likely be explained by our institutional practice of reimaging at 48 hours to assess for pseudoaneuryms. Furthermore, only 2% of patients in the study by Joseph and colleagues received blood products postprophylaxis compared with 13% in our study.

While the transfusion rate did not differ between groups in our study, significantly more units were given to the group receiving early prophylaxis. None of the 4 aforementioned studies demonstrated any significant increase in total blood products given to the early LMWH group as compared with the late LMWH group. Indeed Eberle and colleagues[11] and Datta and colleagues[15] found that those receiving late chemical VTE prophylaxis received more blood products but attributed this to a more injured group at baseline. Our study raises the important issue that patients receiving early chemical VTE prophylaxis may require more blood products than similarly injured patients. It is, however, beyond the scope of a retrospective review to determine the impact of LMWH on the amount of blood transfused, and unknown confounding factors may be present, highlighting the need for a prospective study. The lack of transfusion difference found by Joseph and colleagues[12] is perplexing as our cohorts were very similar in age, sex, ISS and grade of SOI. Therefore, it is unlikely that our study was biased toward sicker patients who may require more supportive care. The patients included in the study by Joseph and colleagues[12] required an average of 2 units (early group) compared with zero units in the intermediate and late groups. This difference was not significant, but the sample size was small. Further the overall use of blood transfusion in the cohort was low at only 2%. Despite this finding, our study adds to the reported literature, suggesting that early chemical VTE prophylaxis is safe in select patients following blunt SOI, as measured by failure of NOM.

The strengths of our study include a relatively large sample size compared with those of other studies in the existing literature and the homogeneous patient population studied, namely patients with blunt SOIs but without significant head injuries. Although the use of

chemical VTE prophylaxis in patients with head injuries appears to be safe, adoption is slow and prospective trials are lacking.[16,17]

### *Limitations*

Limitations of our study are related to the retrospective nature and lack of controlled protocol for chemical VTE initiation at our centre. While patients were similar in age, sex and injury scores, there was a significant difference in the percentage of high-grade splenic injuries, which could be a confounding factor and may highlight a reluctance to initiate chemical VTE prophylaxis in this particular subset of patients, leading to a selection bias that was unlikely to be overcome by using a larger sample size. The event rate for the primary outcome, failure NOM, was low and represents an important limitation. However, our event rate is in keeping with those reported in the other literature on the topic.[9,11,12] The low event rate limits the robustness of our conclusions, but suggests that patient selection for VTE prophylaxis is currently reasonable at our centre with respect to failure of NOM. The rate of VTEs was also low (1.9%) and was similar to those reported in other cohorts, but we do not routinely screen for DVT and PE, and the rate was determined based on confirmed imaging studies. The small number of outcomes ($n$ = 3) makes it challenging to draw meaningful statistical conclusions, but emphasizes the fact chemical VTE prophylaxis is not 100% effective at prevention. Finally we did not assess the role of mechanical VTE prophylaxis in this study. Limitations with regards to blood transfusion require caution in interpreting a greater need in the early group. When measured relative to initiation of chemical VTE prophylaxis, those receiving early therapy appeared to receive more total transfusions, but this may be owing to a lead-time bias.

## Conclusion

Our study adds to the literature supporting early chemical VTE prophylaxis with LWMH in patients with blunt SOIs in the absence of significant head injury. This study showed no difference in NOM failure rates nor any difference in the use of transfusion. The finding that more units of blood may be transfused in patients who receive early VTE is intriguing, and further work to elucidate this association is required. Given this finding and the limitations inherent with retrospective cohort studies, a multicentred prospective study is warranted.

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**Competing interests:** None declared.

**Contributors:** P. Murphy, N. Sothilingam, N. Parry and K. Vogt designed the study. P. Murphy, N. Sothilingam, T. Charyk Stewart, B. Batey and K. Vogt acquired the data, which P. Murphy, N. Sothilingam, T. Charyk Stewart, B. Moffat, D. Gray, N. Parry and K. Vogt analyzed. P. Murphy and K. Vogt wrote the article, which all authors reviewed and approved for publication.

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