Heparin prophylaxis for deep venous thrombosis in a patient with multiple injuries: an evidence-based approach to a clinical problem

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Objective: To demonstrate a clinical decision-making process by which to determine if heparin prophylaxis for deep venous thrombosis (DVT) is appropriate in a specific patient with multiple injuries. **Data sources:** A Medline search of the literature. Search terms included trauma, heparin, deep venous thrombosis, thrombophlebitis, phlebitis, and trauma. **Study selection:** Eleven studies were selected from 789 publications using published criteria.Incidence, risk and potential for prophylaxis were established through a structured review process. **Data extraction:** After the structured review, a small number of studies were available for the consideration of incidence (2), natural history (4) and prophylactic therapy (2). **Data synthesis:** The incidence of DVT in a patient with such multiple injuries is significant (58%–63%). The resulting risk of pulmonary embolism was 4.3% with an associated 20% death rate. Prophylaxis with low molecular weight heparin is associated with a statistically and clinically significant risk reduction for DVT when compared with unfractionated heparin and untreated controls. **Conclusions:** Few of the multiple available studies concerning trauma, DVT and pulmonary embolism meet reasonable standards to establish clinical validity. Available guidelines for literature evaluation allow surgeons to select relevant articles for consideration. Patients with multiple trauma appear to be at significant risk for DVT. The death rate associated with subsequent pulmonary embolism is significant. There is reasonably good evidence to suggest that low molecular weight heparin will reduce this likelihood without a significant risk of treatment complications.

Objectif : Démontrer un processus de prise de décisions cliniques permettant de déterminer si un traitement prophylactique par héparine contre la thrombose veineuse profonde (TVP) convient à un patient atteint de multiples blessures. **Sources de données :** Recherche de documents effectuée dans Medline. Les termes de recherche comprenaient trauma, heparin, deep venous thrombosis, thrombophlebitis, phlebitis et trauma. **Sélection d'études :** Onze études ont été choisies parmi 789 publications en fonction de critères publiés. L'incidence, le risque et la possibilité d'administrer un traitement prophylactique ont été évalués dans un examen structuré. **Extraction de données :** Suite à l'examen structuré, il restait un nombre restreint de documents permettant l'examen de l'incidence (2), de l'évolution naturelle (4) et du traitement prophylactique (2). **Synthèse des données :** L'incidence de la TVP chez un patient présentant de multiples blessures est importante (58 % à 63 %). Le risque d'embolie pulmonaire en découlant s'est établi à 4,3 %, et le taux de mortalité connexe, à 20 %. Le traitement prophylactique faisant appel à l'héparine de faible masse moléculaire entraîne une réduction du risque de TVP significative sur les plans statistique et clinique, comparativement à l'héparine non fractionnée et à l'absence de traitement. **Conclusions :** Peu d'études traitant de traumatismes, de TVP et d'embolies pulmonaires satisfont aux normes raisonnables de validité clinique. Les lignes directrices sur l'évaluation des écrits permettent aux chirurgiens de retenir les articles pertinents pour l'examen. Les patients atteints de multiples blessures semblent très vulnérables à la TVP. Le taux de mortalité associé à l'embolie pulmonaire consécutive à la TVP est important. Des données raisonnablement valables indiquent que l'administration d'héparine de faible masse moléculaire réduira cette probabilité sans exposer les patients à un risque important de complications.

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Trauma is the commonest cause of death for Canadians under 45 years of age. The average national injury admission rate was estimated at 72 per 10 000 people for 1995/1996, and injury-related admissions accounted for 2 187 305 hospital days.[1] The total direct and indirect costs of these injuries has been estimated at Can$14 billion annually.[2] However, the long-term outcome of traumatic injury has not been well documented for individuals nor is the cost to society well defined.

The hospital care of patients with multiple injuries frequently requires coordination among a number of surgical specialists. This can lead to conflict concerning priorities of treatment and risk assessment. One such example is the potential use of heparin prophylaxis to reduce the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) in a patient with multiple injuries resulting from blunt trauma. To address this issue, we present a clinical case with the following management concern: Is heparin indicated to prevent the risk of DVT in a specific patient with multiple injuries? A structured approach to the evaluation of the available clinical literature is illustrated to allow resolution of this specific management concern.

Case presentation

A 43-year-old man was found unconscious in his car after a head-on collision. He was wearing a seat belt. The driver of the other vehicle was dead at the accident scene. The patient was breathing spontaneously, and there was no significant external bleeding. He was reported to be hemodynamically stable. Emergency crews applied a hard cervical collar, extricated the patient from the vehicle and transferred him to a local hospital. There, an endotracheal tube was placed and 1500 mL of crystalloid solution was administered intravenously. The patient was then transferred to the regional trauma centre.

On arrival at the trauma centre, the patient's blood pressure measured 120/70 mm Hg, the heart rate was 74 beats/min and the Glasgow Coma Scale score was 3.[3] His external injuries consisted of bilateral facial lacerations and a left elbow laceration. There were no obvious abnormalities on rectal examination. Gross hematuria was found after catheterization of the bladder. Subsequent investigation included computed tomography of the head, abdomen and pelvis, cystography, and radiography of the chest, pelvis, left elbow and the cervical, thoracic and lumbar spine. These revealed a pelvic fracture involving the right and left pubic rami, the right iliac crest with widening of the sacroiliac joint, an intertrochanteric fracture of the right hip, an extraperitoneal rupture of the bladder, a left hemopneumothorax with 2 rib fractures and a closed head injury associated with a linear nondepressed skull fracture. The injury severity score (ISS) was 14.[4]

After initial assessment in the emergency room, a left-side chest-tube thoracostomy was made and the facial lacerations were sutured. Simultaneous consultation was obtained from the urologic, orthopedic and neurologic surgery services. The bladder rupture was treated with Foley catheter drainage. The right hip fracture was managed by open reduction and internal fixation on the day of admission. At the same time, the left elbow laceration was debrided and closed.

Question: Should this patient be given heparin to prevent deep venous thrombosis?

An informal poll of the staff surgeons and surgical residents from all disciplines attending the University of Ottawa, Department of Surgery rounds, suggested that approximately one-third considered DVT prophylaxis with heparin appropriate for this patient, one-third considered such prophylaxis inappropriate and one-third were uncertain. Few could objectively state whether their opinions were supported by the current medical literature, expert opinion, personal experience or by some other means.

Evidence for prophylaxis: the decision-making process

The decision-making process concerning whether to give heparin for DVT prophylaxis in this patient included the following:

- Consideration of the incidence of DVT after multiple trauma in patients with similar levels of injury severity.
- Consideration of the natural history of DVT in such a patient (clinical sequelae).
- Consideration of the evidence concerning the efficacy of heparin in reducing the risk of clinical sequelae.

Methods

To address these issues we first conducted a Medline search for DVT prophylaxis and trauma. Search terms included DVT, phlebitis, trauma, heparin, and anticoagulation. We discovered 789 publications since 1975 related to this topic. Papers reporting single-system injuries were excluded. The remaining publications were considered if information was available on the incidence of DVT, natural history of DVT or efficacy of heparin prophylaxis for patients with multiple injuries. All publications in each category were then evaluated against published standards (Tables 1, 2 and 3). After considerating the validity of published results, a decision was then made concerning the incidence, natural history and efficacy of intervention to reach a conclusion about the appropriateness of heparin prophylaxis in this patient.

Incidence of deep venous thrombosis after multiple trauma

Incidence of disease refers to the number of new cases of disease in a

population at risk for that disease over a specified period of time. Publications of incidence should follow a well-defined study group prospectively to determine the rate at which new cases of disease appear. We evaluated the literature identified in our search against published standards concerning the determination of incidence in an attempt to establish the potential incidence of DVT in the patient in question (Table 1).[5] In addition, an estimate of incidence might come from untreated control groups in a randomized controlled trial (RCT) of prophylaxis for DVT. Unfortunately no such RCT was available. A review of the articles discovered from our literature search revealed 2 studies that met most of our criteria for inclusion.[6,7]

Both of the identified studies were single-centre prospective evaluations of patients with multiple injuries resulting from blunt trauma (primarily motor vehicle collisions). The patients had a specified ISS similar to the patient's score in our clinical example (> 9) and all had objective documentation of the deep venous system by angiography. Both studies were purely observational. Heparin was not given prophylactically to patients during the study period. The incidence of DVT in these studies ranged from 58% to 63%.[6,7] The DVT was isolated to calf veins in 32% to 40% of patients, and 18% to 32% suffering from DVT of the popliteal and proximal veins. The combined incidence of DVT after multiple injuries resulting from blunt trauma for the 2 study populations was 58%.

These studies suggest that the patient described in this example is at significant risk for DVT. His ISS and mechanism of injury appear to be similar in profile to those described in the reviewed articles. Despite the numerous articles published concerning DVT and trauma, we found only 2 studies with reasonable methodology that could assist us in determining the potential incidence of DVT in patients with multiple trauma when prophylactic therapy is not given. We had a relatively high level of confidence in the conclusion of the studies that DVT is a common sequela of multiple blunt trauma.

Table 1

Evaluation of Articles to Determine Incidence of Deep Venous Thrombosis (DVT)[5]

Question	Considerations
Is the study group defined (specification of denominator)?	Information is required to specify the study population: patients would require injuries to > 1 system, and injury severity scores must be available. To document the true risk of DVT, study patients should not receive heparin prophylaxis.
Is the study prospective?	Accurate determination of incidence would require prospective evaluation of a defined group of patients.
Is objective documentation of DVT available (specification of numerator)?	Diagnosis of DVT requires objective documentation. Articles were selected if patients underwent duplex scanning or venography for diagnosis.
Is the follow-up period defined and adequate?	Incidence rates are stated in terms of a defined period of time. Articles were selected if a defined follow-up period was stated and patient follow-up was comprehensive.

Table 2

Evaluation of Articles to Determine the Natural History of Deep Venous Thrombosis (DVT)[8]

Question	Considerations
Is an inception cohort created?	All patients should enter the study at an early and uniform time in the evolution of disease. Evaluation should be precipitated by initial admission for multiple trauma.
Is the referral pattern described?	How do patients enter the study? Does this affect applicability? Were the evaluated studies conducted in tertiary-care regional trauma centres?
Is there complete follow-up of study patients?	Can we rely of the findings of the study? Were all patients admitted with multiple injuries assessed objectively (duplex scanning or venography) for the development of DVT at an appropriate time?
Are there objective outcome criteria?	Are such criteria available and applied in a uniform manner? Have the authors documented what standards were used to conclude that a diagnostic study was positive for DVT or pulmonary embolism? Can we be certain that these criteria were applied in a uniform manner?
Is assessment of outcome blind?	Those who review outcome criteria should not know of other potential patient factors that might affect outcome. Do the studies document that those interpreting the diagnostic studies for DVT and pulmonary embolism were blinded to the clinical status of the patient and to the results of other diagnostic studies?

Natural history of deep venous thrombosis in patients with multiple trauma

Although the incidence of DVT in patients with multiple trauma appears to be high, this would hold clinical significance only if serious sequelae resulted from the DVT. The natural history of a recognized disease follows a path from the biologic onset of the disease, which may initially be asymptomatic and difficult to diagnose, to a clinical outcome. The outcome resulting from DVT might include an asymptomatic recovery or chronic post-phlebitic syndrome, acute PE and even death. The concern when considering whether or not to give heparin prophylactically for DVT is the prognosis of DVT in the trauma patient. What is the probability that any of these outcomes will occur?

Publications of natural history

should follow a well-defined study group prospectively to determine rates of outcome. We evaluated the literature identified from our search against published standards to select publications that would allow an estimation of the risk of PE and death following DVT in patients with multiple injuries (Table 2).[8] We identified 4 articles on the natural history of DVT that met most of these published criteria.[7,9–11] These studies, which used objective outcome criteria, suggest that although the risk of PE in patients with DVT and multiple injuries was relatively low (0.3%–2.0%), the mortality associated with this outcome was consistently high (20%–23%). Only 1 study evaluated patients who did not receive DVT prophylaxis.[7] This study reported a 4.3% risk of PE associated with DVT and a mortality of 20%.

Critical evaluation of these publications demonstrated that none of the studies reported blind outcome assessment. Only 1 study demonstrated the assembly of a true inception cohort.[7] This was also the only study that was performed in a prospective fashion. Consequently, although our level of confidence in the conclusions reached by these studies might be guarded, there was consistency in the results. PE may occur in up to 4.3% of patients with DVT and multiple injuries, and this event appears to be associated with a high death rate (20%–23.3%). This limited evidence suggests that although PE is relatively uncommon after trauma, a significant mortality is associated with these events. No studies were identified that reported long-term morbidity and mortality.

Is there evidence supporting heparin prophylaxis for this patient?

The literature reviewed suggested that the patient under consideration is at high risk for DVT. There appears to be a definite associated risk of PE, and this event is associated with a high death rate. Consequently, consideration of heparin prophylaxis to prevent these events may be justified.

Our literature search identified 6 prospective therapeutic studies that met our general inclusion criteria.[12–17] Each study was evaluated against these published guidelines (Table 3[18,19]). When we considered only randomized controlled studies with reasonable statistical power, only 2 publications remained for consideration of the use of heparin prophylaxis in patients with multiple injuries and an ISS greater than 9.[13,16] The first study compared the use of low molecular weight heparin (LMWH) to sequential compression devices.[16] Some methodologic concerns of this study include a lack of blinding and complete patient follow-up; however, the study did demonstrate a relative risk of 0.3 for the development of DVT, favouring therapy with LMWH. The second study randomized patients to receive LMWH or unfractionated heparin.[13] There was a definite treatment effect, with a 30% risk reduction for all DVT and a 58% risk reduction for proximal venous thrombosis resulting from use of LMWH. This study had no untreated control group. The authors concluded that LMWH could reduce the risk of DVT when compared to unfractionated heparin. The risk of DVT was considerably lower in patients treated with LMWH than historical untreated control groups. The strengths of this study included complete follow-up and the objective use of a "gold standard" (venography) to document the status of the venous system. This study provides the strongest evidence to date that LMWH decreases the risk of DVT in patients with multiple injuries.

Neither of the studies documented a significant risk associated with use of LMWH in patients with multiple injuries. Patients with frank

Table 3

Methodologic Assessment of Studies Concerning Therapy for Deep Venous Thrombosis (DVT)[12]

Question	Considerations
Was the assignment of patients to treatment randomized?	Are there any studies with randomization?
Were all patients who entered the trial properly accounted for and attributed at the conclusion?	Was follow-up complete? Were patients analyzed in the groups to which they were randomized?
Were patients, their clinicians and study personnel blind to treatment?	
Were the groups similar at the start of the trial?	If the studies were not randomized, is there evidence that the study groups were similar enough with respect to outcome variables that any differences might confidently be attributable to treatment effects alone?
Aside from the experimental intervention, were the groups treated equally?	Did all patients receive the same diagnostic scrutiny for the development of DVT and pulmonary embolism? Were there any other interventions that might affect outcome that differed among the study groups?
How large was the treatment effect?	Was the treatment effect both clinically and statistically relevant? Did the use of heparin reduce the outcome of interest enough to justify clinical interest?
How precise was the estimate of treatment effect?	Were confidence intervals sufficiently narrow to support confidence in any positive findings of the study?
Can the results be applied to the care of my patient?	Were the patients being treated for DVT prophylaxis similar to those of the patient being studied? Were the injuries and treatment settings sufficiently similar that the results might be generalized to the patient in question?
Were all clinically important outcomes considered?	Did the studies address complications of intervention as well as reduction in adverse outcomes such as DVT, pulmonary embolism and death?

intracranial hemorrhage were excluded; however, all other patients with head trauma were included. This has particular relevance to the patient under consideration in this review. Anecdotally, caution might be indicated for patients who have had a craniotomy. One patient treated with LMWH after a craniotomy for a severe skull fracture suffered a subdural hematoma 4 days after surgery. The hematoma required evacuation; the patient made a complete neurologic recovery.

Resolution of patient management

As a result of our structured review of the available literature concerning the use of heparin to reduce the risk of DVT and PE in patients with multiple injuries, the following conclusions can be made:

- The risk of DVT in patients with multiple injuries is significant.
- Although the risk of PE resulting from such a DVT is low, in an individual patient the high overall incidence of DVT and the considerable risk of death associated with subsequent PE suggests that effective prophylaxis would be a clinically relevant intervention.
- LMWH appears to be efficacious in reducing the risk of DVT in patients with multiple injuries similar to the patient in this review.

Recommendation and clinical course

It was recommended that this patient be started on LMWH to reduce the risk of DVT. Postoperatively, the patient was admitted to the intensive care unit and started on LMWH. He regained consciousness and was extubated 6 days after the original injury. He continued to improve clinically and was eventually transferred to a rehabilitation centre 27 days after the injury. There was no sign of DVT on follow-up duplex scanning.

Discussion

The volume of literature available to a treating physician can be conflicting and overwhelming if a structured approach to paper selection and evaluation is not undertaken. Despite the large volume of literature on trauma, DVT and heparin, we were only able to find a few clinically relevant papers that adhered, at least in part, to published guidelines for the evaluation of the clinical literature. The application of these guidelines allowed a review of a reasonable volume of available literature and led to a clinical decision concerning management with a reasonable degree of confidence in the clinical recommendation.

The Eastern Association for the Surgery of Trauma has recently published consensus guidelines for the prevention of venous thromboembolic disease in trauma patients.[20] The consensus panel noted, in agreement with our finding, that the current available evidence regarding the optimal means of prophylaxis is limited by quality. The available evidence was categorized as follows: class I (prospective randomized controlled trials), class II (prospective or large retrospective cohort studies) and class III (small retrospective cohort studies or expert opinion). Unlike our review, however, the panel did not restrict its evaluation to studies on a trauma population. All the available surgical literature concerning DVT prophylaxis was included when the guidelines were developed. On the strength of the evidence, the resulting clinical recommendations were categorized as follows: level I (convincingly justified based on the available scientific evidence alone), level II (reasonably justified) or level III (supported but lacking adequate scientific evidence). Furthermore, a risk stratification tool developed through an empiric consensus process by a group of trauma surgeons was provided. These various risk factors were weighted, and recommendations the various prophylactic measures for thromboembolic events were agreed upon. This consensus group was of the opinion that there was insufficient evidence to support a level I recommendation for the use of LMWH in trauma patients. Such a recommendation would require the availability of large, multicentre, randomized, controlled studies. Such studies are not available. Although we do not disagree with this generalization, it can be difficult to apply generalizations to specific patients. Our review has approached this question from the opposite direction. A patient with a specific clinical problem has been considered against a structured review of the available literature.

Although we would not necessarily generalize our conclusions to all trauma patients, particularly those with significant closed head injury, our treatment recommendation for our specific patient appears to be justified. It is interesting to note that a risk-factor assessment tool for venous thromboembolism in trauma was also proposed by the consensus committee. Based on their empirical risk scoring system, our trauma patient would have received a risk score of 9 (pelvic fracture = 4, GCS score < 8 = 3, surgical procedure > 2 h = 2). This score would have supported the use of LMWH in this case. The consensus panel did also urge that each institution should adopt local guidelines based on risk assessment for DVT and potential complications of heparin therapy. The final decision to use heparin prophylaxis in this patient resulted from a structured review of the best available literature related to similar patients. In particular, we felt that the demonstrated high risk of DVT and the low risk of reported complications associated with the use of heparin prophylaxis in this population is justified.

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