

# Venous thromboembolism prophylaxis in patients with traumatic brain injury

## *Profilaxia de tromboembolismo venoso em pacientes com lesão cerebral traumática*

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### A B S T R A C T

Traumatic brain injury (TBI) with associated intracranial hemorrhage (ICH) occurs frequently in trauma. Trauma patients are also at high risk of developing venous thromboembolic (VTE) complications. Low Molecular Weight Heparin (LMWH) is used in trauma patients as prophylaxis to reduce the risk of VTE events. It remains unclear, however, if LMWH is safe to use in trauma patients with ICH for fear of hematoma progression. The "Evidence-based telemedicine: trauma & acute care surgery (EBT-TACS)" Journal Club performed a critical appraisal of 3 recent and most relevant studies on timing to initiate, safety and use of LMWH in trauma patients with ICH. Specifically, we appraised a i) critical literature review on the topic, ii) a multicenter, retrospective cohort study assessing the safety of LMWH in trauma patients with ICH and iii) a randomized, pilot study assessing the feasibility and event rates of ICH progression, laying the groundwork for future randomized controlled trials (RCT) on the topic. Some results are conflicting, with the highest level of evidence being the pilot RCT demonstrating the safety for early use of LMWH in TBI with ICH. Much of this research, however, was generated by a single center and consequently lacks external validity. Furthermore, clinical recommendations cannot be generated based on pilot studies. Evidence-based guidelines and recommendations could not be made at this time, until the completion of further studies on this challenging topic.

**Key words:** Wounds and injuries. Craniocerebral trauma. Intracranial hemorrhages. Venous, thromboembolism. Heparin, low-molecular-weight.

### INTRODUCTION

The risk of Venous Thromboembolic (VTE) disease is high in trauma patients. There are many controversies surrounding the timing to initiate pharmacological prophylaxis against VTE events in patients with Traumatic Brain Injury (TBI). Low Molecular Weight Heparin (LMWH) is effective for prophylaxis in trauma patients. Many patients, however, present with intracranial hemorrhage (ICH) as part of their traumatic brain injury. In these patients the use of LMWH is controversial, for fear of progression of the ICH<sup>1,2</sup>. A recent meta analysis published by Hamilton *et al.*<sup>3</sup> calculated that for every 1000 patients undergoing elective craniotomy who receive pharmacologic VTE prophylaxis, 91 VTE events will

be prevented, while 7 episodes of iatrogenic hemorrhage expansion will occur. Although this data is helpful, it must be interpreted with consideration of its limitations for applicability to trauma. The TBE-CITE Journal Club performed a critical appraisal of the most important evidence published recently on the topic and provides evidence-based recommendations on the safety, efficacy, timing and patient selection for VTE prophylaxis in TBI patients.

### STUDY 1

Pharmacologic Venous Thromboembolism Prophylaxis after Traumatic Brain Injury: A Critical Literature Review<sup>4</sup>

**EBT-TACS Journal Club: October 30<sup>th</sup>, 2012, with the participation of the following institutions:** Division of Trauma & Surgical Critical Care, Department of Surgery, Miller School of Medicine, University of Miami, Miami, USA; Division of Trauma Surgery, Department of Surgery, Faculty of Medical Sciences, University of Campinas, Campinas, SP, Brazil; Trauma Program of the Department of Surgery of Sunnybrook Health Sciences Center, University of Toronto, Toronto, Canada.

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### Rationale

Despite the frequency and morbidity of VTE after traumatic brain injury, no standard of care exists to guide caregivers on the use of prophylactic anticoagulation. The development of VTE after TBI carries with it the potential for significant complications; however, the timing to initiate prophylaxis in TBI is controversial, given the risk of progression of associated ICH. The present review critically assessed the literature on this topic by examining the existing evidence on safety and efficacy of pharmacologic VTE prophylaxis in the setting of elective craniotomy and after TBI. To this end, the author proposes his own protocol, which stratifies patients into low, moderate and high risk for the likelihood of natural progression of the pattern of hemorrhage, allowing one to tailor a unique VTE prophylaxis regimen to each group of patients.

### Question

What is the evidence demonstrating safety and efficacy for VTE prevention, using LMWH strategies for TBI patients?

### Main Findings

There are the most important findings of this study:

1. No standard of care or defined VTE prophylaxis best practice exists to guide TBI caregivers for the use of prophylactic anticoagulation. Research has been generally limited to observational/ retrospective studies.
2. VTE is well known to be a time-dependent phenomenon.
3. It is consensus that early initiation of VTE prophylaxis is risky for renewing bleeding in TBI, however "early/ late time periods" are yet to be better defined.
4. The current patients' dichotomization (absence or presence of intracranial hemorrhage) is criticized and the Parkland Protocol (which stratifies patients into low, moderate and high risk of spontaneous expansion) is presented.

### Strengths

- Critical literature review and appraisal of the available evidence.
- Debates / critiques the current measures for pharmacologic VTE prophylaxis.
- Suggests future directions for pharmacologic VTE prophylaxis.
- Propose a Bern-Norwood modified protocol, which stratifies patients into low, moderate and high risk.

### Limitations

- Due to low level of evidence available this research reviews mainly observational studies and retrospective studies.
- The "Parkland Protocol" is not proven to be effective and may not be validated for application in other centers.

- Clinical findings are not considered in the proposed protocol.

## STUDY 2

Is low-molecular-weight heparin safe for venous thromboembolism prophylaxis in patients with traumatic brain injury? A Western Trauma Association (WTA) multicenter study<sup>5</sup>

### Rationale

LMHWH has shown to be superior to mechanical and low-dose heparin for the prevention of DVT in injured patients. However, the safety of using LMHWH in trauma patients sustaining ICH remains undetermined. There is reluctance to the use of LMHWH in this specific trauma population due to concerns about ICH progression. The Western Trauma Association conducted a large multisite retrospective study in order to investigate the safety of VTE prophylaxis with LMWH in patients with traumatic ICH.

### Question

Is VTE prophylaxis with LMWH in patients with traumatic ICH safe?

### Main Findings

1. Close to 20% of the entire study sample had received LMWH despite having a concomitant ICH.
2. Trauma patients with ICH who received LMWH were different from controls. Specifically, those patients tended to be more severely injured, with a lower Glasgow Coma Score (GCS) on admission. They also required more urgent neurosurgical intervention within 24 hours compared to controls for bleeding progression.
3. Trauma patients administered LMWH had an increased rate of progression of their ICH.
4. The timing to initiate LMWH had no effect on ICH progression. In other words, giving LMWH later (after 48 hours or 7 days of admission) was the same as giving LMWH early (within 48 hours of admission).
5. More VTE events occurred paradoxically in the LMWH group, compared to controls.

### Strengths

- This study looked at a large number of patients from several Level I trauma centers. Events were noted in both interventional and control groups and although not powered formally (this is a descriptive study), a type II error is unlikely.
- This study addresses a very important question in trauma regarding the safety of LMWH in patients with ICH. It is an important study to generate testable hypotheses regarding the use of VTE prophylaxis in trauma, especially

with LMWH. Further studies can now be designed to test these hypotheses further.

### Limitations

· The study populations used for comparison were different. The group receiving LMWH had more severe ICH, required more neurosurgical interventions and were more injured overall, with longer hospital length of stay, making it difficult to draw any conclusions.

· The increased rate of VTE events in the LMWH group further demonstrated the marked differences between the groups

· ICH progression measured by head CT alone has its limitations and clinically relevant information such as changes in neurological status should also be included.

· The absence of significant difference in the rate of ICH progression based on LMWH timing lacks biological plausibility (< 48 hours has the same progression as one week later). Due to the retrospective nature of this study, the temporal correlation between initiation of LMWH and ICH progression is lacking. Furthermore, differences in risk factors for ICH progression among subgroups were not reported. Finally, the subgroup analysis involved small cohort, making difficult to draw any definitive conclusion.

Overall, this multicenter retrospective cohort study demonstrates the urgent need for randomized controlled trials, with patient characteristics randomly distributed between both control and interventional group to draw more reliable conclusions.

## STUDY 3

A randomized, double-blinded, placebo-controlled pilot trial of anticoagulation in low-risk traumatic brain injury: The Delayed Versus Early Enoxaparin Prophylaxis I (DEEP I) study<sup>6</sup>

### Rationale

The timing to initiate VTE chemoprophylaxis in TBI is controversial, given the risk of progression of ICH. Different institutions use different algorithms that are supported by weak evidence and often consider TBI as a binary clinical state – either with or without ICH. This approach does not account for the known fact that the risk of progression may differ with the initial ICH volume. The authors tested a hospital-based protocol that stratifies patients into low, medium or high risk for spontaneous bleeding progression and tailors VTE prophylaxis to each arm (Parkland Protocol). This pilot RCT focused on early versus delayed VTE chemoprophylaxis initiation in the low risk group of TBI patients. It was conducted to generate point estimates of the rate of worsening of the intracranial

hemorrhage after initiation of enoxaparin or placebo. The present study was designed as a pilot for future RCT to evaluate the safety and efficacy of the Parkland protocol.

### Question

Does the early initiation of VTE chemoprophylaxis in patients with pre-specified small and stable TBI patterns lead to radiographic worsening of the TBI pattern? Secondary outcomes were extra cranial hemorrhage complications and VTE occurrence.

### Main Findings

CT scan progression of the bleeding occurred in 5.9% of the low risk patients receiving early enoxaparin versus 3.6% of those on placebo. This difference did not reach statistical significance. Clinically, no difference could be detected between the groups. There was no extra-cranial bleeding complications with a single symptomatic deep vein thrombosis in a patient in the placebo arm. The authors conclude that this pilot study demonstrated that the randomization of TBI patients based on the hospital-based algorithm is feasible and provides point-estimates of the rate of worsening intracranial hemorrhage.

### Strengths

· Multicenter (two hospitals) randomized controlled pilot trial, double blinded with intention-to-treat analysis.

· Binary radiological and clinical outcomes measured, which can assist clinicians in clinical management of patients.

· Neuroradiologists were blinded to treatment arms

· Adjudication was carried out for conflicting interpretations.

· Non-inferiority analysis conducted based on a 5% margin

· The superior 'Gwet AC1 statistic' was used, not Kappa, for inter-rater reliability.

· Prolonged follow-up time was proposed for the secondary outcomes.

### Limitations

· Pilot RCT not powered to conclusively answer whether early VTE chemoprophylaxis is safe and efficacious. Only feasibility and point estimates could be generated.

· Only two hospitals tested the protocol, which limits the validity of the study.

· GCS score on admission was not reported, which may be predictive of risk of progression.

· The rate of ICH progression in low risk TBI population is significantly different from that reported in the literature. Studies by Narayan *et al.*<sup>7</sup> and Allard *et al.*<sup>8</sup> found a 50% progression of contusion volume at 24 hours compared to baseline CT.

. The association between the radiological progression of the ICH with clinical deterioration of the patients is not specified.

. Would trauma surgeons and other clinicians be comfortable with a trial design where CT scans are done on an as needed basis and dictated by changes in neurological status?

. No explanation about the 'gold standard' read by the neuroradiologists.

. Initial exclusion of "other" patients were not clear, or the reasons for the significantly higher rate of field intubation in the placebo group, suggesting the groups could be different

. Other notable difference between groups included a 2 times higher rate of *prn* head CT scans in patients receiving enoxaparin. This finding also raises questions on whether the clinicians were blinded to treatment allocation

. Screening for DVTs should have been included both symptomatic and asymptomatic DVTs. The true rate of DVTs may have been underestimated by testing only symptomatic patients.

Overall, this pilot RCT demonstrated point estimates of rates of worsening intracranial hemorrhage in preparation for a future definitive RCT. Caution should be exercised in drawing any clinical conclusions from this pilot RCT since it was underpowered for clinically relevant outcomes when comparing enoxaparin to placebo in early VTE prophylaxis in low risk TBI patients.

## R E S U M O

*Traumatismo crânio-encefálico (TCE), com hemorragia intracraniana associada (HIC) ocorre com frequência em trauma. Pacientes vítimas de trauma também estão em alto risco de desenvolver complicações venosas tromboembólicas (TEV). Heparina de Baixo Peso Molecular (HBPM) é utilizada em pacientes de trauma, como profilaxia para reduzir o risco de eventos de TEV. Ainda não está claro, no entanto, se a HBPM é segura para uso em pacientes com trauma com HIC por receio da progressão do hematoma. O Clube de Revista "Telemedicina Baseada em Evidências: Cirurgia do Trauma e Emergência (TBE-CITE)" realizou uma apreciação crítica de três estudos recentes e mais relevantes no tocante ao momento de início da profilaxia, à segurança e ao uso de HBPM em pacientes com trauma e HIC. Especificamente, três estudos foram revisados: i) uma revisão crítica da literatura sobre o tema, ii) um estudo multicêntrico, estudo de coorte retrospectivo avaliando a segurança de HBPM em pacientes com trauma, e com HIC e iii) um estudo piloto randomizado, avaliando a viabilidade e as taxas de eventos de progressão de HIC, servindo como base para futuros ensaios clínicos randomizados (ECR) sobre o tema. Alguns resultados são conflitantes, com o maior nível de evidência sendo o ECR piloto demonstrando a segurança para o uso precoce de HBPM no TCE associado com HIC. Grande parte desta pesquisa, porém, foi gerada por um único centro e, conseqüentemente, carece de validade externa. Além disso, as recomendações clínicas não podem ser geradas com base em estudos-piloto. Diretrizes baseadas em evidências e recomendações não podem ser feitas, neste momento, até a realização de outros estudos sobre este assunto desafiador.*

**Descritores:** Ferimentos e lesões. Traumatismos craniocerebrais. Hemorragias intracranianas. Tromboembolia venosa. Heparina de baixo peso molecular.

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## CONCLUSIONS

The studies reviewed by the EBT- TACS Journal Club included a critical review of the literature, a multicenter retrospective cohort trial and a multicenter pilot RCT (DEEP I). Each one evaluated either the safety, efficacy and timing to initiate prophylaxis or point estimates for the use of LMWH in patients with TBI and ICH. The publications differ methodologically and in their conclusions. The literature review highlights the urgent need for evidence-based guidelines. The multicenter trial from the WTA calls for caution in LMWH administration due to ICH progression despite the analysis being done on patient populations that were not equal. Results from the DEEP I pilot RCT demonstrated an event rate of progression of ICH that was similar between intervention (LMWH) and placebo groups. Two of the 3 studies were performed in the same hospital proposing the same hospital-based protocol.

### Recommendations

Both VTE and ICH progression in trauma patients with TBI are devastating events. Despite one study (pilot RCT) suggesting it is safe to initiate LMWH early in patients with TBI and ICH who are deemed low risk for progression of hemorrhage, the group decided that no recommendation could be done at this time on the safety, efficacy and timing to initiate chemoprophylaxis in these patients. Better evidence is urgently needed on this topic.

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#### STATEMENT

The opinions and assertions contained herein represent the private views of the participants of the Evidence-based Telemedicine - Trauma and Acute Care Surgery (TBE - CITE) Journal Club, and are not to be construed as reflecting the views of the institutions that they represent.

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