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A Systematic Review of the Benefits and Risks of Anticoagulation Following Traumatic Brain Injury

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Abstract

Objective—The objective of the study was To synthesize the existing literature on benefits and risks of anticoagulant use after traumatic brain injury (TBI).

Design: Systematic review—A literature search was performed in Medline, IPA, Health Star and CINAHL on October 11, 2012 and updated on September 2, 2013, using terms related to TBI and anticoagulants.

Main Measures—Human studies evaluating the effects of post-TBI anticoagulation on venous thromboembolism (VTE), hemorrhage, mortality or coagulation parameters with original analyses were eligible for the review. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed throughout the conduct of the review.

Results—Thirty-nine eligible studies were identified from the literature, of which 23 studies with complete information on post-TBI anticoagulant use and patient outcomes were summarized in this review. Meta-analysis was unwarranted due to varying methodological design and quality of the studies. Twenty-one studies focused on the effects of pharmacological thromboprophylaxis (PTP) post-TBI on VTE and/or progression of intracranial hemorrhage (ICH) while two RCTs analyzed coagulation parameters as the result of anticoagulation.

Conclusion—PTP appears to be safe among TBI patients with stabilized hemorrhagic patterns. More evidence is needed regarding effectiveness of PTP in preventing VTE as well as preferred agent, dose and timing for PTP.

Introduction

An estimated 1.7 million traumatic brain injuries (TBIs) occur annually in the United States, causing 52,000 deaths, 275,000 hospitalizations and 1,365,000 emergency department visits yearly.¹ Patients with TBI are at increased risk of developing venous thromboembolism (VTE) due to their prolonged immobilization and hypercoagulable state.²⁻⁵ Denson et al reported a VTE incidence of 25% in patients experiencing isolated TBI, compared to 2% in all trauma patients and 18% in high risk patients, and suggested that early prophylaxis against VTE was warranted among TBI patients.⁶ The incidence of VTE may be as high as 54% among patients with major head trauma not treated with mechanical or pharmacological prophylaxis.⁷ However, anticoagulation treatment is complicated by the possibility of exacerbated bleeding in trauma patients. While the risks of intracranial bleeding and systematic bleeding have historically been the major concern of implementing prophylactic anticoagulation among patients with TBI,^{8,9} some studies have shown that anticoagulation is safe in patients with normal coagulation and stable intracranial hemorrhage (ICH) patterns.¹⁰⁻¹⁴

There is not a standard of care guiding the use of anticoagulant agents post TBI. The guideline for management of severe TBI cites level III evidence for using low molecular weight heparin (LMWH) or low dose unfractionated heparin (LDH) in combination with mechanical prophylaxis, but the guideline provides no recommendations with respect to which subgroups of TBI patients might benefit more from prophylactic anticoagulation and the preferred agent, timing and dose.⁹ A recent narrative review on pharmacological

thromboprophylaxis (PTP) after TBI categorized the existing literature into studies treating TBI patients as a homogeneous population and studies considering TBI patients as a heterogeneous population, and discussed the findings from the literature.¹⁵ The review did not consider the issue of resumption of anticoagulants among patients chronically treated with anticoagulants and management of those patients. This could be due to the fact that the scope of the review was restricted to PTP or it could indicate an information gap. Pre-injury use of anticoagulation adds more controversy to management of TBI patients as it exposes patients to higher risk of hemorrhage.^{16,17} A systematic review with an extended scope to chronic anticoagulant use is needed for identifying knowledge gaps. This literature review systematically gathers and synthesizes published evidence on the benefits and risks of anticoagulation post TBI.

Methods

The conduct and reporting of the present systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁸

Eligibility criteria

Human studies evaluating the effects of post TBI anticoagulation on VTE, hemorrhage, mortality or coagulation parameters with original analyses were eligible for the review. Studies were required to include, but not restrict the patient population to, TBI patients. Reviews, case reports, guidelines and studies reported in languages other than English, Chinese or Arabic were excluded.

Information source and search strategy

Medline, International Pharmaceutical Abstracts, Health Star and Cumulative Index to Nursing and Allied Health databases were initially searched up to October 11, 2012. The search was updated on September 2, 2013. The search terms included MeSH terms and/or keywords related to TBI and anticoagulants. MeSH terms for TBI included “Brain Injuries”, “Head Injuries, Closed”, “Head Injuries, Penetrating”, “Intracranial Hemorrhage, Traumatic”, “Skull Fractures” and “Coma, Post-Head Injury” and keywords included “Trauma”, “Brain”, “Head” and “Skull”. MeSH terms for anticoagulants included “Anticoagulants”, “Coumarins”, “Heparin” and “Antithrombins” and keywords included the names of anticoagulants that were ever on the market or in clinical investigations at the time of the search.

Study screening

Studies were screened for their eligibility by four pairs of reviewers (Y.Z. & X.L., J.P. & M.A., S.D. & Z.K., B.K. & X.S.). Reviewers were paired up based on educational background to ensure each pair contained at least one person with clinical expertise and one person with research experience. A hierarchy of exclusion criteria was developed and used by the reviewers for screening studies (Figure 1). The reviewers first screened titles and abstracts of the studies yielded from the database searches. The full text of studies deemed potentially relevant was retrieved for a full review. For both rounds of screening, studies were split among the four pairs of reviewers. The two reviewers in each pair reviewed the

same studies independently and any discrepancies regarding the eligibility of studies that could not be resolved between the two were brought to the full study team for a decision. Reference lists of relevant reviews and included studies were reviewed by B.K. and X.S. to identify additional studies.

Data collection

The eight reviewers abstracted data from the eligible studies using a structured table created by the study team. The accuracy of abstracted data was checked by S.K., Z.K. and X.S.. The data items collected included: study objective, study design, country, eligibility criteria, sample size, treatment arms, setting, duration of follow up, and results. If any of these data items were not reported in the manuscript, the study authors were contacted via email to obtain the information.

Assessment of study quality

Quality of individual studies was assessed based on Downs and Black checklist by S.K.D., J.B.P., and Y.T.. The Downs and Black checklist is an instrument for evaluating methodological quality of both randomized and non-randomized studies.¹⁹⁻²² The checklist consists of five domains, including reporting, external validity, bias, confounding, and power. An average of the three reviewers' scoring was calculated for each study.

Results

Study selection

The database searches yielded 1,026 unique studies, of which 114 were retrieved for full-text review. Based on the full text review, 10 case reports/series, 4 letters to editor, 2 reviews, 18 studies lacking TBI patients, 42 studies lacking a focus on post TBI anticoagulation and 1 study with irrelevant outcomes were excluded. One decision analysis and 1 duplicate publication were further excluded. Three additional studies were identified from the reference lists. One more study was found from the search update. A total of 39 eligible studies were included in the present review (Figure 2).

Study characteristics

Among the 39 studies that met the inclusion criteria, 16 studies are not presented in this review due to lack of information on post TBI anticoagulant use and patient outcome.^{3,23-37} A majority of these studies were interested in patients with any trauma and the information specific to the subset of TBI patients could not be obtained.^{3,23,26-29,32,33,36} The remaining 23 studies were summarized in Table 1 ([Supplemental Digital Content](#)). Among these 23 studies, 3 were randomized controlled trials (RCTs), 4 were prospective cohort studies and 16 were retrospective cohort studies. A majority of studies focused on the effects of PTP post TBI on VTE and/or hemorrhagic progression (n=21), and 2 RCTs evaluated coagulation parameters as the outcome.^{38,39} Of those 21 studies on PTP, 7 had no control group,^{13,14,40-44} 6 studies compared PTP with no PTP,^{8,12,45-48} 3 studies compared enoxaparin to another anticoagulant agent,^{10,49,50} and 5 studies evaluated the timing of prophylaxis.^{11,51-54} On a scale of 27, only one out of the 23 studies scored ≥ 20 and six

scored ≥ 18 on the Downs and Black checklist (Figure 3). The reviewers determined that meta-analysis was unwarranted due to heterogeneous study design and quality.

Anticoagulation versus no anticoagulation

Scudday et al (quality score: 17) studied the efficacy and safety of a PTP protocol in 812 TBI patients.¹² The protocol required a standard administration of PTP to all patients without ICH progression at the 24-hour follow-up computed tomography (CT) and recommended sequential compression device (SCD) for all patients. The protocol also suggested twice weekly Duplex ultrasound screening for VTE for patients not receiving PTP, but the screening was performed rarely in both the PTP and the non-PTP groups. Three patients (1%) in the PTP group and 11 (3%) in the non-PTP group developed VTE. After controlling for age, Injury Severity Score (ISS), Abbreviated Injury Score (AIS) head and neck and Glasgow Comma Scale (GCS) score, the relative risk (RR) for developing VTE was 0.19 (95% CI: 0.05-0.76) comparing patients on PTP to those not on PTP. The rate of ICH progression was not statistically significantly different between the two groups: 11 patients (3%) receiving PTP and 25 patients (6%) not receiving PTP experienced ICH progression (adjusted RR=0.47, 95% CI: 0.22-1.02). The authors concluded that PTP in TBI patients with stable or improved head CT after 24 hours of injury reduced the incidence of VTE without increasing the risk of ICH progression.

Similar observations regarding safety of PTP among patients with stabilized hemorrhagic patterns were made by Phelan et al (quality score: 20) and Levy et al (quality score: 18).^{8,46} Phelan et al conducted a pilot randomized trial with an analysis of non-inferiority to examine the effects of prophylactic enoxaparin on progression of ICH among low-risk TBI patients. More specifically, TBI patients presenting within 6 hours of injury with small injury patterns and stabilized CT scans at 24 hours were considered having low risk. Patients on anticoagulants before the injury were excluded from the trial. Sixty-two patients were randomized to either enoxaparin 30 mg every 12 hours from 24 to 96 hours after injury or placebo. ICH progression based on CT at 24 hours after initiation of enoxaparin was found in 2 patients [5.9%, 95% confidence interval (95% CI: 0.7-19.7%)] in the enoxaparin group and 1 patient (3.6%, 95% CI: 0.1-18.3%) in the placebo group. The difference in ICH progression between the two groups was non-significant (2.3%, 95% CI: -14.4-16.5%). One symptomatic DVT occurred in the placebo group while none occurred in the enoxaparin group.

Levy et al categorized 340 TBI patients with varying injury severity into 248 patients with a stable initial follow-up CT within 24 hours of admission and 92 patients with ICH progression on initial follow-up CT. Eighteen (7.3%) and 29 (31.5%) patients in these two groups experienced a subsequent ICH progression during hospitalization. Multivariable logistic regression showed that PTP was significantly associated with ICH progression in patients with ICH progression on the initial CT after adjusting for other risk factors, but such association was absent among patients with a stable initial CT.

While the majority of included studies evaluated anticoagulant use in level I trauma centers, Carlile et al (quality score: 19) evaluated prophylactic anticoagulation during rehabilitation in TBI patients aged 16 years or older.⁴⁵ The study sample consisted of 1,897 patients, 932

of whom received PTP and 965 did not. Incidence of symptomatic VTE was low in both the PTP and non-PTP groups (1.6% vs. 1.8%, respectively). After propensity score adjustment, the odds ratio (OR) for symptomatic VTE was 0.80 (95% CI: 0.33–1.94) comparing those who received PTP to those who did not. Three patients (0.3%) in the PTP group developed or experienced an expansion of ICH versus 12 patients (1.2%) in the non-PTP group. Systemic hemorrhage occurred in 4 (0.4%) patients in the PTP group and 2 (0.2%) patients in the non-PTP group. Two randomized trials that used coagulation parameters as study outcomes showed that administration of antithrombin concentrate slowed coagulation among TBI patients.^{38,39} Eachempati et al (quality score: 13) studied the effects of anticoagulation in treatment of 23 patients with blunt vascular injuries to the head and neck BHVI,⁴⁷ among whom 13 patients had concurrent closed head injury (CHI). Four out of the 13 CHI patients received heparin 48 hours after injury and 4 received long-term warfarin. No bleeding events occurred to any of the 13 CHI patients.

Head-to-head comparison of anticoagulation

Dudley et al (quality score: 18.3) conducted a retrospective head-to-head comparison between PTP with enoxaparin and PTP with dalteparin on VTE and ICH progression rates among 287 moderate to severe TBI patients (post-resuscitation GCS score 3-12).¹⁰ PTP was initiated 48-72 hours after injury if a patient had two consecutive CT scans indicating hemorrhage stability and continued until the patient was fully ambulatory. All non-ambulatory patients were placed on mechanical prophylaxis unless contradicted. The incidence of VTE was similar between patients treated with enoxaparin (n=9, 7.0%) and those treated with dalteparin (n=12, 7.5%) with no significant difference between the groups (p=0.87). The mean time to VTE was 20.1 days and 15.6 days for the enoxaparin and dalteparin group, respectively. Only 1 patient in enoxaparin group had a symptomatic expansion of an existing ICH, which led directly to death.

Two retrospective cohort studies compared enoxaparin with unfractionated heparin (UFH). Minshall et al (quality score: 16.7) studied 386 TBI patients and found no statistically significant difference in deep vein thrombosis (DVT) between patients on prophylactic enoxaparin (n=1, 1%), those on prophylactic UFH (n=2, 1%) and those without PTP (n=1, 2%). The UFH group had significantly higher rate of pulmonary embolism (PE) than the enoxaparin group (n=7, 4% vs. n=0, 0%, p<0.05) as well as higher rate of ICH progression (n=20, 12% vs. n=5, 5%, p<0.05). However, no statistical adjustment was made to account for the more severe patients in the UFH group. The study by Arnold et al (quality score: 16.3) included 99 CHI patients with significant ICH.⁴⁹ Patients were treated with either enoxaparin or low-dose UFH for VTE prophylaxis. There was no significant difference in VTE incidence between the UFH group and the enoxaparin group (n=8, 17.0% vs. n=6, 11.5%, p=0.57).

Early vs. late anticoagulation

Salottolo et al (quality score: 19) not only evaluated the effects of PTP among adult patients with blunt TBI, but examined the impact of timing and continuity of PTP on clinical outcomes.⁵³ Starting PTP within 72 hours of admission was considered early initiation of PTP, while starting PTP 72 hours or after was considered late initiation. Interrupted PTP

was defined as any interruption in PTP. A total of 15 patients (3.2%) developed VTE, 20 (4.2%) died, and 47 (9.8%) had hemorrhage progression. After controlling for concurrent severe injury in chest and extremities, AIS head score, GCS score, pre-injury blood thinner use and gender, neither timing of PTP (early vs. late adjusted OR=2.00, 95% CI: 0.39-10.27) nor continuity of PTP (interrupted vs. continuous adjusted OR=7.07, 1.08-46.36) was found to be associated with VTE.

Koehler et al (quality score: 17.3) examined early versus late PTP with enoxaparin among 669 TBI patients with an AIS head/neck score of at least 3.¹¹ No adjustment was made to control for the confounding that the patients in the late PTP group were more severely injured than those in the early group. Timing of prophylaxis was defined as early (<72 hours following hospital admission) or late (>72 hours). Univariate analyses showed no statistical difference between the early and late groups in incidence of proximal DVT (n=4, 1.5% vs. n=14, 3.5%, p=0.12), distal DVT/superficial venous thrombosis (n=10, 3.7% vs. n=27, 6.7%, p=0.10) or PE (n=4, 1.5% vs. n=9, 2.2%, p=0.49). The rate of ICH progression before initiation of PTP was significantly lower in the early group than in the late group (n=45, 9.4% vs. n=136, 17.4%, p<0.0001). Such a relationship was not observed for ICH progression after initiating PTP (n=7, 1.46% vs. n=12, 1.54%, p=0.91). Kim et al (quality score: 17) also focused on severe TBI and found similar rates of post PTP DVT (early vs. late: n=2, 4% vs. 1, 6%) and PE (early vs. late: n=2, 4% vs. 0, 0%) among the 64 patients included in the study.⁵¹ Depew et al (quality score: 13.7) and Reiff et al (quality score: 16) also evaluated the effects of PTP timing on the outcomes,^{52,54} but statistical analyses were not performed to demonstrate whether the differences in the rate of VTE or ICH progression were significant between groups receiving PTP with different timing.

Studies without comparison groups

Seven observational studies without comparison groups were identified from the literature. Two studies by Norwood et al (quality score: 12.7 and 15) demonstrated rates of VTE and ICH progression lower than 2% and 4%, respectively, among TBI patients treated with early enoxaparin prophylaxis.^{13,14} Similar rates were reported by Kim et al (quality score: 15), Kleindienst et al (quality score: 15.7) and Pahatouridis et al (quality score: 11.7).^{40,41,43} Unlike other studies, O'Brien et al (quality score: 15) focused their study on pediatric and adolescent population.⁴² The study sample included a subset of 144 patients with head injuries, among whom VTE occurred to 5 patients (3.5%). The study by Senft et al (quality score: 13.3) included 107 TBI patients who underwent surgical treatment of subdural hematoma (SDH).⁴⁴ Outcomes were only reported for the 11 patients who were on oral anticoagulants before injury. Six-month mortality for those 11 patients was 45.5% although none underwent a second surgical procedure resulting from re-bleeding.

Discussion

The existing evidence on benefits and risks of anticoagulation post TBI is weak. A majority of the studies we found in our review were observational, a design which is subject to selection bias and limits the ability to make causal inferences. Further, most studies were restricted to inpatient VTE prophylaxis and none of the included studies examined

resumption of long-term anticoagulant among patients taking anticoagulants chronically before TBI.

For TBI patients treated with PTP, the incidence of VTE (range: 0% to 17.4%) as well as the incidence of ICH progression (range: 0% to 12%) varies greatly (Table 1). This variation might partially be due to differences in outcome measures (i.e. symptomatic vs. subclinical) among studies. For example, ultrasound screening for DVT was routinely performed based on the institution policy in the Arnold et al study⁴⁹ while DVTs were solely diagnosed by clinical exams and confirmed by ultrasound in the Minshall et al study.⁵⁰ Another explanation for the observed variation in VTE and ICH progression rates could be the differences in selection of patient population across the studies. In other words, studies that included patients of greater injury severity or with unstable hemorrhage patterns were more likely to find higher rates of VTE and ICH progression than those studies restricted to patients with small and/or stable injury patterns. The differences in the choice of outcome measures and study populations might also partially explain why Denson et al⁶ and Geerts et al⁷ observed much higher incidence of VTE for TBI patients than the studies included in this review. The Denson et al study only included TBI patients at high risk for VTE who underwent weekly lower-extremity venous surveillance. The Geerts et al study also had a surveillance system in place to detect VTE among the major head trauma patients participated in the study.

The variation in VTE and ICH progression rates implies heterogeneity of TBI patients and suggests the need for crafting guidelines for use of anticoagulation based on patients' risks for developing VTE and progression of existing injury. Hemorrhagic stability is commonly considered an important criterion for assessing risk of ICH progression. Phelan et al and Scudday et al showed that PTP did not increase the incidence of ICH progression among patients with stable hemorrhage patterns.^{12,46} The study by Levy et al stressed the importance of ensuring stability of hemorrhage patterns before initiating PTP.⁸ The study demonstrated that PTP was safe among patients with a stable CT at 24 hours of admission but it would expose patients with initial ICH progression to a 13-fold higher risk of worsening ICH. It seems that the finding that PTP is safe among TBI patients with stable hemorrhage patterns can be extended to those who suffered moderate-to-severe TBI. In the study by Dudley et al, symptomatic ICH expansion only occurred to 1 of the 287 moderate to severe TBI patients who initiated LMWH prophylaxis after 2 or more consecutive stable CT scans.¹⁰

There is limited evidence regarding the benefits of PTP for preventing VTE in the population with stabilized hemorrhage patterns. The study by Scudday et al is the only study that showed a favorable effect of PTP on VTE prevention among this low-risk population (adjusted RR=0.19 (95% CI: 0.05-0.76)).¹² Although the two studies by Norwood et al found that the incidence of DVT was less than 2% among patients with small and stable injury patterns and treated with early PTP, the conclusion that PTP was beneficial in reducing VTE cannot be drawn due to the lack of comparison groups.^{13,14} TBI itself is an independent risk factor for VTE,^{2,49,52} therefore studies choosing to study patients with small and stable injury patterns are likely to find a lower incidence of DVT in the first place. However, despite the differences in patient selection and outcome measures used, it still seems

reasonable to believe that PTP is effective in preventing VTE among TBI patients given the substantial reduction in VTE incidence from 54% reported in Geerts et al study for patients not treated with any form of prophylaxis to 0%-17.4% observed by the studies included in the review for patients treated with at least PTP. Stronger evidence is needed to conclude the effectiveness of PTP in reducing VTE for TBI patients.

Enoxaparin was compared with UFH and dalteparin regarding efficacy of preventing VTE and risk of ICH progression. Two studies found that there was no statistically significant difference in the outcomes between enoxaparin and UFH/dalteparin.^{10,49} Minshall et al found that patients receiving enoxaparin had fewer PE events, fewer cases of ICH progression and lower mortality than the UFH group.⁵⁰ However, they also found that the mean ISS and AIS head were higher in the UFH group than the enoxaparin, suggesting that differences seen in the outcomes were likely at least partially due to the imbalance in injury severity between the two treatment groups.

The question when to start anticoagulation in TBI patients cannot be answered with the existing evidence from the literature. Five studies evaluated the effects of PTP timing on VTE and ICH progression; however, three of these studies provided descriptive results only.^{51,52,54} Both the Koehler et al and the Salottolo et al studies showed no difference in ICH progression post initiation of PTP.^{11,53} Koehler et al found that ICH progression before starting PTP occurred more frequently in the late PTP group than in the early PTP group (early vs. late: 9.4% vs. 17.4%).¹¹ This finding indicates that selection bias might exist in clinical practice where physicians tend to delay PTP for patients at higher risk for ICH progression. In addition, the study found particularly low rates of ICH progression after initiating PTP (early vs. late: 1.46% vs. 1.56%). Such results do not necessarily suggest that PTP is safe among TBI patients. More likely, it implies that attending physicians withhold PTP for TBI patients until the risk for ICH progression subsides.

The only study in a rehabilitation setting found no difference in VTE incidence between patients who received PTP and those who did not, after propensity score adjustment.⁴⁵ However, 5.5% of 1,075 patients screened positive for DVT at admission to rehabilitation, which suggests the potential value of PTP for TBI patients transitioning from hospitals to rehabilitation centers. There is insufficient evidence in the literature on the safety of resuming long-term anticoagulation after TBI or guidance in management of those patients taking oral anticoagulants before injury. Only Eachempati et al evaluated long-term anticoagulation, but the focus of the study was on blunt vascular injuries to the head and neck (BHVI) rather than TBI.⁴⁷ Three studies specifically excluded patients on pre-injury anticoagulation.^{11,43,46} The Senft et al study identified 11 patients who were on pre-injury oral anticoagulation, but they did not report any information regarding oral anticoagulant use after injury.⁴⁴

Conclusion

The decision to use anticoagulants following a TBI should be made based on whether the benefits of anticoagulation outweigh the risks in at the patient level. PTP appears to be safe among TBI patients at low risk of developing a new hemorrhage or experiencing

progression of an existing hemorrhage, however, future studies are required for confirmation. Overall, the quality of the existing literature is heterogeneous. Better evidence is needed regarding efficacy of PTP in preventing VTE as well as preferred agent, dose and timing for PTP. Future studies should consider further adjustment in parameters such as TBI severity and use of AC prior to injury in order to ensure comparability of study groups. In addition, future research investigating long-term management of patients with pre-injury use of anticoagulants is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflict of Interests and Source of Funding

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Figure 1.
Hierarchy of Eligibility Criteria Used for Screening Studies

Figure 2.
Flowchart for Study Selection

Figure 3.
Methodological Quality Scores by Study