Thromboprophylaxis for trauma patients (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Thromboprophylaxis for trauma patients

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of thromboprophylaxis in trauma patients on mortality and incidence of DVT and PE.

To compare the effects of different thromboprophylaxis interventions and their relative effects according to the type of trauma.

BACKGROUND

Description of the condition

Trauma is one of the leading causes of death and disability in young people (Evans 2003). Worldwide, about five million people die as a result of trauma every year (WHO 2008). For patients who reach hospital within one hour of trauma (called the 'golden hour'), blood loss and traumatic brain injury are the main causes of death (Sauia 1995). For patients who survive beyond the first day, multiple organ failure, central nervous system (CNS) failure and venous thromboembolism (VTE) are the principal causes of death (Acosta 1998).

Trauma patients are at known risk of entering into a hypercoagulable state. Mechanisms of hypercoagulability in the trauma setting include stasis, vessel wall dysfunction and alterations in clotting mechanisms (Virchow's triad). Injured patients are often immobilized after high-energy trauma. Being in a static position causes a reduction in venous blood returns and a decrease in the supply of oxygen and nutrients to endothelial cells. In addition, endothelial damage caused by direct trauma to the vessels causes the exposition of tissue factor bearing cells. This initiates a procoagulant factor that amplifies the coagulant response. These tissue factor bearing cells move to the cell surface of the platelets, which produces a propagation of the signal through the accumulation of thrombin, activated cofactors and more platelets, inducing thrombosis (Hoffman 2001).

On the other hand, trauma patients experience a reduction of fibrinolytic pathways that seems to result from increased plasminogen activator inhibitor (PAI) 1. PAI 1 inhibits tissue plasminogen activator (tPA) and thus decreases the production of plasmin (Rogers 1995; Kelsey 2000). Coagulation abnormalities and the reduced ability to use the muscular pump of the calf in the injured patient can produce deep venous thrombosis (DVT) in the inferior and superior extremities (Spaniolas 2008). When the thrombus extends to the proximal segments, there is an increased risk of clot migration to the lungs and a fatal outcome (Geerts 2008).

Trauma patients are at high risk for DVT, with an incidence of 11.8% to 65% (Sevitt 1961; Geerts 1994; Velmahos 2000). The incidence varies according to the method used to measure the DVT and the location of the thrombosis. Incidence of thrombosis in the thigh (proximal DVT) is estimated at 18% (Geerts 1994). The incidence of pulmonary embolism (PE) is estimated between 1.5% and 20% (Shackford 1988; O'Malley 1990; Velmahos 2000). Many risk factors for DVT and PE in trauma patients have been identified, such as spinal cord injury; lower extremity and pelvic fractures; need for surgical procedures; increasing age; femoral venous line insertion or surgical repair of venous injuries; prolonged immobility; long duration of hospital stay; severity of the trauma and mechanism of injury (Geerts 1994; Knudson 1994; Frezza 1996; Velmahos 2000; Cipolle 2002; Rogers 2002; Meissner 2003).

Description of the intervention

Thromboprophylaxis describes any intervention used to prevent the development of VTE, and can be categorized into mechanical and pharmacological interventions.

External mechanical devices such as graded compression devices or intermittent pneumatic compression (IPC) have been shown to be effective in preventing DVT, but they cannot be used in patients with lower extremity trauma (Fisher 1995; Elliott 1999; Velmahos 2000). Internal mechanical devices are used to prevent the migration of thrombus from DVT to the lungs, thus preventing PE. One such device is the inferior vena cava filter (IVCF) which may be particularly useful in trauma patients because of the risk of ongoing bleeding at injured sites (McMurty 1999).

Pharmacological thromboprophylaxis was first described in the 1940s by Bauer 1944, and since then a number of interventions have been proposed. The anticoagulant effect of unfractionated heparin (UH) is initiated by the activation of antithrombin III (ATIII). The ATIII/heparin complex inactivates the thrombin factor IIa, and factors Xa, IXa, XIa and XIIa. However, UH is associated with a number of adverse events, such as thrombocytopenia. More recently, alternatives such as low molecular weight heparin (LMWH), a derivative of UH, have been proposed. LMWH acts in the same way as UH, but its low molecular weight fragments reduce the binding to other cells and proteins (and it also has a major affinity to factor Xa) (Hirsh 2004). These drugs have potential as effective prophylactic interventions for trauma, although there is concern due to the associated increased risk of bleeding (Geerts 1996; Haentjens 1996; Knudson 1996; Cohn 1999). Other methods of thromboprophylaxis, such as anticoagulants (warfarin) or antiplatelets (aspirin), seem less practical for use in critically ill patients, because of their delayed action and oral presentation. Pentassacharides (a new class of synthetic selective factor Xa inhibitor, with parenteral presentation which does not bind to platelets, other cells or proteins) have been studied as prophylaxis in surgical orthopedic patients and have been shown to be as effective as UH and LMWH (Nijkeuter 2004).

How the intervention might work

Due to prolonged rest and coagulation abnormalities, trauma patients are at an increased risk of thrombus formation. Thromboprohylaxis, either mechanical or pharmacological, may decrease the mortality and morbidity in trauma patients who survive beyond the first day treated in hospital, decreasing the risk of DVT and PE in this population. A previous Cochrane review focusing on high-risk patients indicated that combined methods (pharmacologic and mechanical interventions) decreased the incidence of DVT (Kakkos 2008). However, this systematic review did not examine the effects in the subgroup of trauma patients.

Why it is important to do this review

Trauma patients are at an increased risk of VTE, and thromboprophylaxis has the potential to be effective in this population. However, trauma patients are at an increased risk of bleeding, one of the adverse events associated with pharmacological interventions. For some trauma patients with injured extremities, the use of mechanical interventions (e.g. external mechanical compression) is not feasible. A previous systematic review (Velmahos 2000) did not find evidence of effectiveness for either pharmacological or mechanical interventions. However, this systematic review was conducted 10 years ago and most of the included studies were of poor quality. Since then new trials have been conducted. Although current guidelines (Rogers 2002; Geerts 2008) recommend the use of thromboprophylaxis in trauma patients, there has not been a comprehensive and updated systematic review since the one published by Velmahos and collaborators. Furthermore, there are still uncertainties about the relative benefit of interventions for different subgroups of trauma patients. Therefore it is necessary to conduct a systematic review to establish whether the effect of different thromboprophylaxis interventions varies according to the type of trauma, location of the trauma, severity of trauma and type of management (surgical or medical management).

OBJECTIVES

To assess the effects of thromboprophylaxis in trauma patients on mortality and incidence of DVT and PE.

To compare the effects of different thromboprophylaxis interventions and their relative effects according to the type of trauma.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials.
If we identify randomized cross-over trials, we will include data from the first experimental period only.

Types of participants

Patients of any age with any type of trauma. We will exclude trials that only recruited outpatients, trials that only recruited elderly patients with hip fractures, or patients with acute spinal cord injuries.

Types of interventions

We will include trials reporting the use of any of the following methods:

1. Unfractionated heparin (UH).
2. Low weight molecular heparin (LWMH).
3. Mechanical methods: graded compression stocking, and sequential compression devices.
4. Oral anticoagulants (i.e. warfarin).
5. Antiplatelet drugs (i.e. aspirin).
6. Pentassacharides.
7. Pulmonary embolism prophylaxis (i.e. inferior vena cava filter (IVCF)).

We will compare the effects of any intervention with placebo, and any two interventions (e.g. LMWH versus UH) or combination of interventions (UH plus mechanical methods versus UH).

Types of outcome measures

Primary outcomes

The primary outcomes will be mortality, incidence of DVT and PE.

Secondary outcomes

The secondary outcomes will be the incidence of adverse events, such as:

- bleeding (major and minor);
- whether the adverse event (bleeding of the injured site, intracranial bleeding, gastrointestinal bleeding, epistaxis, etc.) required transfusion or any procedure to control it;
- and other adverse events as defined by the study authors.

Search methods for identification of studies

We will not restrict searches by date, language or publication status.

Electronic searches

We will search the following electronic databases:

- Cochrane Injuries Group Specialised Register (to latest version);
- Cocnrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue);
- MEDLINE (Ovid SP) (1950 to most recent date available);
- EMBASE (Ovid SP) (1980 to most recent date available);
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to most recent date available);
- ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to most recent date available);
- ZETOC (to most recent date available);
- LILACS (BIREME) (1982 to most recent date available);
- PubMed (www.ncbi.nlm.nih.gov/sites/entrez/) (to most recent date available).

We will base searches on the MEDLINE search strategy listed in Appendix 1, and adapt it to the specifications of each of the other databases.

Searching other resources

We will search the reference lists for all relevant material and for further potentially eligible studies. We will search the Internet using the Google (www.google.com) search engine with selected terms from the above strategy to identify any further unpublished or grey literature. We will browse the following clinical trials websites for complete and ongoing trials:

- www.clinicaltrials.gov;
- Controlled Trials *meta*Register (www.controlled-trials.com).

Data collection and analysis

Selection of studies

Two authors (LB and PP) will independently examine titles, abstracts, and keywords of citations from electronic databases for eligibility. We will obtain the full text of all potentially relevant records and two authors will independently assess whether each meet the pre-defined inclusion criteria. We will resolve any disagreement through discussion with a third author (CM). If there is ambiguous or missing information, the authors will contact investigators of the study to clarify study eligibility.

Data extraction and management

Two authors (LP and PP) will extract data independently, using a standardized data extraction form. LB will enter the extracted information into Review Manager for analysis (RevMan 2008). We will extract data on the following characteristics.

1. General Information: title, authors, source of publication, country, published or not, language and year of publication.
2. Trial characteristics: study design and information that meets The Cochrane Collaboration's tool for assessing risk of bias.
3. Participants: sample size, inclusion criteria, exclusion criteria, location of trauma (brain, chest, abdomin, pelvis, extremity, polytrauma), severity of trauma (ISS, RTS, or according to the scale used by the trialists), type of injury (blunt or penetrating), and type of surgical procedure (non-operative or surgical management).
4. Intervention: type and dose of thromboprophylaxis used, type and dose of control or placebo used.
5. Outcomes: incidence of mortality, incidence of DVT (symptomatic or asymptomatic) and diagnostic test used, incidence of PE and diagnostic test used. Incidence of adverse events as follows: any bleeding, major bleeding defined as use of transfusion or any procedure to control bleeding (bleeding from the injured site, gastrointestinal bleeding, brain bleeding, epistaxis, etc.) and minor bleeding. And other outcomes recorded by the trialists.
6. Results: number of patients in each group, missing patients.
7. Subgroup characteristics: number of patients by localization of trauma, by severity, by type (blunt or penetrating), by type of management (surgical or non-surgical).
8. Other information: funding source.

Assessment of risk of bias in included studies

Two authors (LB and PP) will assess the risk of bias of each included study according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We will assess the following: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. We will complete risk of bias tables based on the above criteria. These will incorporate the review authors' judgement ('Yes' for low risk of bias; 'No' for high risk of bias, or 'Unclear') and description of the design, conduct or observations that underlie the judgement, for each domain in each included study. We will resolve any disagreement by consulting a third author (CM).

Measures of treatment effect

Dichotomous data: We will calculate risk ratios (RR) and 95% confidence intervals (CIs). We will also calculate number needed to treat (NNT) and number needed to harm (NNH).

Continuous data: We will calculate the mean difference (MD) and 95% CIs when the same scale is used in a similar manner across studies. If results for continuous outcomes are reported using different scales or different versions of the same scale, we will calculate the standardised mean difference (SMD) and 95% CIs.

Dealing with missing data

We will attempt to contact the study authors for missing information.

Assessment of heterogeneity

We will examine trial characteristics in term of participants, interventions and outcomes for evidence of clinical heterogeneity. We will examine statistical heterogeneity by both the I^2 statistic and Chi^2 test. The I^2 statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity; substantial heterogeneity is considered to exist when I^2 is larger than 50%. For the Chi^2 test, we will use a P value of less than 0.10 to indicate the presence of statistically significant heterogeneity.

Assessment of reporting biases

We will assess reporting bias using funnel plots.

Data synthesis

If the included trials are clinically homogeneous and there is no evidence of statistical heterogeneity then we will conduct a meta-analysis. For dichotomous outcomes, we will use the Mantel-Haenszel fixed effect method. For continuous outcomes we will use the fixed-effect inverse-variance method.

Because different effects are expected according to the intervention, we will perform data synthesis separately for each type (e.g. UH, LWMH or mechanical devices).

If there is any evidence of clinical or statistical heterogeneity, we will not conduct a meta-analysis, but will instead present the results in a narrative form.

Subgroup analysis and investigation of heterogeneity

If there are sufficient data we plan to perform the following subgroup analyses:

- type of trauma (blunt, penetrating);
- location of the trauma (brain, chest, abdominal, pelvis, extremity or polytrauma);
- severity of trauma defined with ISS or other similar scores;
- management (surgical or medical management);
- diagnostic method.

Sensitivity analysis

We will perform a sensitivity analysis to investigate whether the conclusions are robust. We will examine the effect of excluding certain studies according to their risk of bias. We will report the data synthesis for all the included studies and will repeat the calculations after excluding studies judged as having a high risk of bias for allocation concealment. We will also examine the effect of reporting a different effect measure (odds ratio) for the dichotomous outcomes.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy

MEDLINE 1950 to April Week 3 2009

1.exp "Wounds and Injuries"/
2.(wound* or trauma* or injur* or fracture* or burn* or stab* or shot* or shoot* or lacerat* or accident*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3.1 or 2
4.exp Venous Thromboembolism/
5.exp Venous Thrombosis/
6.exp Pulmonary embolism/
7.exp Thrombophlebitis/
8.(thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or thromboph*).ab,ti.
9.(deep* adj3 (vein* or ven*) adj5 (thromb* or embol*)).ab,ti.
10.((pulmonary or lung*) adj3 (thromb* or embol*)).ab,ti.
11.(DVT or PE or VTE).ab,ti.
12.4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13.(thromboprophylaxis or prophylactic* or prophylaxis).ab,ti.
14.exp Heparin/
15.exp Heparin, Low-Molecular-Weight/
16.exp Heparinoids/
17.exp Stockings, Compression/
18.exp Intermittent Pneumatic Compression Devices/
19.exp Stockings, Compression/
20.exp Anticoagulants/
21.exp Warfarin/
22.exp Platelet Aggregation Inhibitors/
23.exp Aspirin/
24.Heparin*.ab,ti.
25.((compression or impulse or pneumatic or elastic*) adj3 (device* or stocking* or hose* or dressing* or bandage*)).ab,ti.
26.(Anticoagulant* or Warfarin or Coumadin* or apo-warfarin or gen-warfarin or warfant or Coumadin or aldocumar or tedicumar).ab,ti.
27.(Antiplatelet* or (platelet* adj3 aggregation adj3 inhibit*) or ((blood or platelet*) adj3 (antagonist* or antiaggrega*))).ab,ti.
28.(Aspirin* or acetylsalicylic acid or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin or acetysal).ab,ti.
29.exp Vena Cava Filters/
30.((vena adj3 cava adj3 filter*) or (umbrella adj3 filter*)).ab,ti.
31.(Pentassacharide* or fondaparinux).ab,ti.
32.or/13-31
33.randomi?ed.ab,ti.
34.randomized controlled trial.pt.
35.controlled clinical trial.pt.
36.placebo.ab.
37.clinical trials as topic.sh.
38.randomly.ab.
39.trial.ti.
40.33 or 34 or 35 or 36 or 37 or 38 or 39
41.(animals not (humans and animals)).sh.
42.40 not 41
43.3 and 12 and 22 and 42

HISTORY

Protocol first published: Issue 1, 2010

DECLARATIONS OF INTEREST

None known.