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REVIEW ARTICLE

Thromboprophylaxis in trauma : a review of methods, evidence and guidelines

Peter G. VAUGHAN-SHAW, Paul PAVLOU, Joseph G. MANJALY, Peter WARD

From Dorset County Hospital, UK

Venous thromboembolism is a common cause of morbidity and mortality in trauma patients. Mechanical and pharmacological methods of thromboprophylaxis are available and guidelines relating to thromboprophylaxis in trauma include those published by the American College of Chest Physicians, the UK-based National Institute of Clinical Excellence, the Scottish Intercollegiate Guidelines Network and US-based Eastern Association for the Surgery of Trauma. All four guidelines have in common a recommendation for the use of low-molecular-weight heparin except where contraindicated. However, there is little consensus between guidelines relating to which mechanical methods should be used. Given the risk of thromboembolism in trauma patients and increasing interest in this condition clinicians should be aware of local and national guidelines relating to venous thromboembolism prevention in trauma patients. This paper reviews methods of thromboprophylaxis and compares guidelines relating to their use in trauma patients.

Keywords : trauma ; DVT ; PE ; thromboembolism ; thromboprophylaxis ; thrombosis ; heparin.

INTRODUCTION

Trauma is the leading cause of death in people under the age of 40 years (*14*) and fatal pulmonary embolism is the third most common cause of death in patients with major trauma who survive the first 24 hours (*15*). Knowledge of the incidence, morbidity, mortality and pathogenesis of venous thromboembolism (VTE) has led to the development of numerous prophylactic options, methods of risk assessment and guidelines relating to their use. This paper aims to review methods of venous thromboembolism prophylaxis and compares guidelines relating to their use in trauma patients.

Importance, Incidence and Pathogenesis of VTE in Trauma Patients

The importance of venous thromboembolism prophylaxis has been acknowledged by surgeons for over half a century. It has been shown that without prophylaxis deep vein thrombosis (DVT) occurs in over 20% of patients having major sur-

■ Peter G. Vaughan-Shaw, MBChB, BSc (Hons), MRCS (Eng), Core Trainee in Surgery.
Southampton University Hospitals NHS Trust, Southampton, UK.
■ Paul Pavlou, MBBS, BSc (Hons), MRCS (Eng), Specialist Registrar in Trauma and Orthopaedics.
■ Peter Ward, MBChB, MD, FRCS (Tr&Orth), Consultant Orthopaedic Surgeon.
Dorset County Hospital Foundation Trust, Dorchester, UK.
■ Joseph G Manjaly, MBChB, BSc (Hons), Core Trainee in Surgery.
Salisbury NHS Foundation Trust, Salisbury, UK.
Correspondence : Mr Peter Ward, Department of Orthopaedic Surgery and Trauma, Dorset County Hospital, Williams Avenue, Dorchester, Dorset, DT12JY, United Kingdom. E-mail : peter.ward@dchft.nhs.uk

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gery and over 40% of patients having major orthopaedic surgery (*37*). Meanwhile the association of DVT with trauma was noted by Bauer as long ago as 1944 (*4*). The effects of VTE last long beyond the presenting symptoms with post-thrombotic syndrome, venous insufficiency, persistent lung perfusion defects and pulmonary hypertension occurring not infrequently (*30,34,35*). The costs of investigation and treatment, prolonged hospital stay and long-term anticoagulation add to the morbidity of VTE, while the patient risks potentially serious bleeding whilst anticoagulated. The effects on a young, active, working population could be even more devastating. The American College of Chest Physicians (ACCP) states that among hospitalized patients, those recovering from major trauma have among the highest risks for VTE. Without thromboprophylaxis, patients with multisystem or major trauma have a DVT risk that exceeds 50%, and PE is the third-leading cause of death in those who survive beyond the first day (*13*). The stated incidence in trauma patients varies greatly, due in part to the vast heterogeneity in patient demographic and injury, as well as the detection method used. Some indication of incidence can be gained from early case series and randomised control trials. For example a series of 39 polytrauma patients subjected to at least 10 days bed rest reported a DVT incidence of 61.5% (*14,28*) while three randomised control trials reported DVT incidence of 11, 14.5 and 28% in patients with pelvic fractures, acute spinal injury and leg fracture fixation respectively (*1,10,54*). A large meta-analysis conducted by the Agency for Healthcare Research and Quality in the US reported pooled incidence rates of 11.8% and 1.5% for DVT and PE respectively in a trauma population (*51*).

The pathogenesis of VTE in trauma patients follows Virchow's description of almost two centuries ago in which change to blood vessel walls, blood flow and blood viscosity predispose to thrombosis (*53*). The initial insult as well as the trauma of subsequent surgery may cause direct vascular trauma as well as an inflammatory response that may stimulate changes in vessel wall ; the trauma, surgery and the subsequent immobility results in a change towards non-laminar blood flow and venous stasis ; and finally a period of dehydration related to the trauma or a period of 'nil by mouth' together with a post-traumatic hypercoagulability results in a pro-thrombotic state (*33*).

VTE prevention

Knowledge of the incidence, morbidity, mortality and pathogenesis of VTE has led to the development of numerous prophylactic options, methods of risk assessment and guidelines relating to their use. Current prophylactic options can be categorized into mechanical, pharmacological and ancillary. Ancillary methods are those that should occur in all patients, namely early mobilization and prevention of dehydration. The most commonly stated guidelines include those published by the American College of Chest Physicians (ACCP) (*13*), the UK based National Institute of Clinical Excellence (NICE) guideline 92 (*36*), the Scottish Intercollegiate Guidelines Network (SIGN) guideline 62 (*43*) and US-based Eastern Association for the Surgery of Trauma (EAST) guideline (*40*).

Mechanical Thromboprophylaxis

Mechanical prophylaxis includes graduated compression stockings (GCS), intermittent pneumatic calf compression (IPC), venous foot pumps, and inferior vena cava (IVC) filters.

Graduated compression stockings, in common with IPC and venous foot pumps aim to improve venous return from the lower extremities. A large meta-analysis has shown graduated compression stockings to reduce post-operative DVT in general surgical patients but no randomised trials have been performed in a trauma population (*56*). However two studies comparing GCS with GCS and venous foot pumps in elective and emergency hip arthroplasty patients reported DVT incidence as high as 40% when GCS alone were used (*11,45*).

The role of Intermittent Pneumatic calf Compression, also called intermittent sequential compression devices, to simulate exercise or mobilisation were first described by Hills *et al* in 1972 (*19*). IPC aims to increase femoral venous flow and may also increase plasma fibrinolytic activity (*6,24*). These devices employ a sequential pattern

of compression with various chambers being sequentially inflated for 10-12 seconds every minute. Few studies have examined the role of IPC in trauma patients. Dennis *et al* demonstrated a reduction in DVT from 8.8% to 2.7% when compared to no prophylaxis in 395 trauma patients (*7*) while Fisher *et al* showed a significant reduction from 12% to 4% in patients with hip fractures when compared to no prophylaxis (*10*). However no studies have compared IPC to GCS alone in a trauma setting although in all surgical patients, a meta-analysis by Vanek has demonstrated a 47% reduction in relative risk of DVT given IPC compared to GCS alone (*49*). However, a large meta-analysis published subsequently by Velmahos *et al* found that IPC offered no benefit over no prophylaxis (*52*). Further account must be taken of the difficulties and complications of IPC use owing to the presence of lower limb fractures, traction, casts and external fixators in addition to the potential to cause pressure necrosis, compartment syndrome and peroneal neuropathy (*29,38*).

The final and most recently developed non-invasive mechanical method of thromboprophylaxis is the foot pump or Arterio-Venous (AV) boot. This method mimics the plexus of veins discovered by Gardner and Fox that fills by gravity and empties upon weight-bearing (*12*). Despite a number of trials illustrating effectiveness in elective orthopaedic surgery, no level 1 evidence exists for their use in trauma patients. However a non-randomized study in trauma patients by Spain *et al* (*44*) reports that foot pumps are comparable to SCD where SCD are contra-indicated while Knudson *et al* found foot pumps used in a trauma population to be comparable to both LMWH and SCD (*27*). Furthermore a randomised control trial by Fordyce and Ling demonstrated a significant reduction in DVT with foot pumps and GCS when compared with GCS alone in elective hip replacement (*11*). The main benefit is that foot pumps can be applied where fractures, casts or external fixators preclude the use of IPC or GCS. However foot pumps can present similar wound and skin complications to those seen with IPC (*27*).

Guidelines relating to these three methods of mechanical thromboprophylaxis in trauma patients are variable and unclear. The new NICE guideline indiscriminately recommends any one of GCS, IPC or foot pumps without recognition of their variable efficacy or mention of the role of combining various methods. The ACCP recommends 'mechanical prophylaxis with IPC or possibly with GCS alone' and does not include foot pumps in their recommendations. Meanwhile, the SIGN guidelines state 'in (trauma) patients with contraindications to LMWH, mechanical methods can be considered.' Finally the EAST guidelines, which do not mention GCS, conclude that 'there is insufficient data at this time that IPC decreases the risk of VTE in multiply injured patients' and that 'A-V foot pumps may be used as a substitute for IPC in those high risk trauma patients who cannot wear IPCs due to external fixators or casts.' In reflection of the inconsistent evidence, it can be seen that no guideline offers a hierarchy of efficacy of the available mechanical methods. In the presence of some evidence reporting high DVT incidence with GCS used alone, it would seem that a combination of GCS and either IPC or foot pumps would be a sensible approach where not contraindicated.

The final method of mechanical prophylaxis is Inferior Vena Cava filters which are placed to prevent pulmonary emboli in the presence of DVT, recurrent PE, or in high risk patients where pharmacologic and alternative mechanical prophylaxis is contraindicated. While there is good evidence for their efficacy (*16*) only two trials have randomized high risk trauma patients to IVC filters or alternative methods of prophylaxis (*17,25*). Both studies recommend the use of IVC filters in high risk trauma patients demonstrating no pulmonary emboli and few complications in the experimental group. In a detailed review, Velmahos *et al* conclude that 'prophylactic placement of IVC filters in selected trauma patients may decrease the incidence of pulmonary embolism' but concedes that further research is required (*52*). Given this, it is not surprising that guidelines differ in their recommendations. A review of the role of IVC filters by the ACCP quotes a meta-analysis of prospective studies that found no difference in the rates of PE among trauma patients with and without prophylactic IVC filters (*32*) and concludes that given the lack of direct

evidence of efficacy, the high cost and possible complications involved, they do not recommend the use of an IVC filter as thromboprophylaxis. EAST and NICE however recommend consideration of IVC filters in high-risk patients where anticoagulation is contraindicated while the SIGN guidelines do not make mention of IVC filters.

Pharmacological Thromboprophylaxis

Pharmacological methods of thromboprophylaxis include aspirin, warfarin, unfractionated heparin and most commonly low-molecular-weight heparins. Important considerations for their use include increased bleeding risk and reversibility, both especially relevant in trauma patients. The cost of widespread adoption of prophylactic anticoagulation is also a consideration.

The role of Aspirin in reducing thrombosis has been recognised for almost half a century (*41*). The prospect of an effective agent that is inexpensive, easily administered and that does not require laboratory monitoring is attractive. A large meta-analysis published in 1994 reported a statistically significant 39% and 64% odds reduction of DVT and symptomatic PE respectively with the use of any anti-platelet regimen with or without heparin (*2*). Meanwhile the Pulmonary Embolism Prevention (PEP) trial reported a significant reduction in DVT, non fatal and fatal PE in 13356 patients undergoing surgery for hip fracture and 4088 patients who underwent elective knee or hip arthroplasty randomized to treatment with aspirin 160 mg or placebo (*39*). Importantly, however, the use of LMWH or mechanical types of thromboprophylaxis did not preclude entry into the PEP trial and in patients undergoing hip fracture surgery receiving LMWH there was no reduction in VTE rate with aspirin. Furthermore there was no overall difference in total number of deaths at 35 days post-operatively. The limitations of these two papers are reviewed comprehensively by Hovens *et al* (*20*) who conclude that while the use of aspirin is associated with a reduction in postoperative thromboembolism risk it has been surpassed in efficacy by other anticoagulants.

The use of Warfarin in hip fracture surgery was reported as early as 1961 (*42*). While correctly dosed warfarin is an effective thromboprophylactic agent (*22*), the need for laboratory monitoring, delayed onset and offset of action, difficulty of reversal, increased bleeding events and interactions with other medications render it unsuitable for an acute trauma admission.

Heparin, now almost a century from its discovery (*21*), is a widely used thromboprophylactic agent. Since the first randomised trial of heparin in 1960 (*3*) a large number of trials have investigated the efficacy of heparin in preventing VTE. A large meta-analysis by Clagett *et al* reported a reduction in DVT in general surgical patients treated with low dose heparin from 25.2% to 8.7% (*5*) but a number of randomized trials since then have found little evidence for the use of low dose heparin (LDH) (*7,26*). Furthermore two meta-analyses of LDH use in trauma patients have showed no benefit of LDH on incidence of VTE (*48,52*). Evidence for the efficacy of low-molecular-weight heparin (LMWH) is widespread however. The most significant trials relating to its use in trauma patients are those of Geerts *et al* and Knudson *et al* (*15,27*). Geerts *et al* reported a 30% relative risk reduction with LMWH when compared to LDH while Knudson *et al* reported a DVT rate of just 0.8% with LMWH. Neither paper reported a significant increase in major bleeding with LMWH.

A more recently available pharmacological thromboprophylactic agent is the synthetic selective factor Xa inhibitor Fondaparinux which given its specificity is less likely than heparin to cause thrombocytopaenia (*55*). Eriksson *et al* demonstrated a reduction of VTE risk of 56.4% compared with enoxaparin (a LMWH) in a large number of patients undergoing hip fracture surgery (*9*). Furthermore there was no difference in major bleeding or transfusion requirement. More recently Fondaparinux has been shown to be effective in a high risk trauma population with only one patient (1.2%) developing a DVT (*31*). Despite these findings, uptake of fondaparinux remains relatively poor. Cost, timing of the first dose, bleeding side effects, duration of administration and lack of a reliable reversing agent are the likely reasons for this (*23*).

Guidelines relating to the use of pharmacologic prophylaxis are more consistent than for mechanical

methods. The NICE, ACCP, EAST and SIGN guidelines universally recommend the use of LMWH whilst advising against the use of aspirin alone in any patient group. Furthermore, the above guidelines all recognise the unsuitability of warfarin in an acute trauma setting although the ACCP does suggest that in the setting of prolonged rehabilitation associated with decreased mobility there is a role for warfarin. LDH is not recommended for use as a sole agent by the ACCP or EAST, yet NICE does suggest LDH may be used in patients with renal failure where benefits outweigh potential bleeding risk. Finally, given the lack of class 1 evidence in general trauma patients, the ACCP and NICE only recommend the use of Fondaparinux in hip fracture surgery and state that administration should be delayed until primary haemostasis has been demonstrated. The SIGN and EAST guidelines which are considerably older give little mention to Fondaparinux.

All guidelines refer to the risk of bleeding with pharmacologic prophylaxis and recognise that both bleeding risk (Table I) and VTE risk must be considered when prescribing thromboprophylaxis. The ACCP guideline discusses a number of papers including a randomised control trial by Greenfield (*17*) and a large Cochrane review (*18*) which both fail to demonstrate an increased risk of bleeding with LMWH or LDH. The timing of pharmacologic prophylaxis is also an important issue and more complicated in trauma than elective patients where the injury as well as the surgical procedure may confer a bleeding risk. NICE offers the clearest advice, recommending restarting LMWH or LDH 6-12 hours after surgery yet it is clear that all decisions must be made on an individual basis.

Finally, a new class of oral anticoagulant is now selectively available but not mentioned by any of the above guidelines. Dabigatrin and other fixed dose oral thrombin inhibitors which do not require regular monitoring are now licensed in the UK for thromboembolism prevention following elective hip and knee arthroplasty. Pending further research and license extension, these may become important agents in trauma thromboprophylaxis, particularly in an outpatient setting.

Table I – Risk factors for bleeding, taken from NICE guideline 92, '*Venous thromboembolism: reducing the risk.*'

Risk factors for bleeding
• Active bleeding
• Acquired bleeding disorders (such as acute liver failure)
• Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ratio [INR] higher than 2)
• Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
• Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
• Acute stroke
• Thrombocytopenia (platelets less than 75×10^9/l)
• Uncontrolled systolic hypertension (230/120 mmHg or higher)
• Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

DISCUSSION

Principal findings

More than 65 years after the association of DVT with trauma was reported by Bauer, some inconsistency remains in recommendations for prevention of thromboembolism in trauma patients. All four guidelines studied have in common a recommendation for the use of LMWH except where contraindicated. However, there is little consensus between guidelines relating to which mechanical methods should be used (see Table II) which reflects similar inconsistency in the literature. That the NICE guideline gives most emphasis to mechanical methods and the need to consider bleeding risk, is likely to be due to the representative panel of orthopaedic surgeons that was involved at every stage of its development (*47*). This was perhaps a result of disputes between the ACCP and the American Academy of Orthopaedic Surgeons relating to the ACCP guideline (*8*) and concerns raised by the British Orthopaedic society relating to the previous NICE guideline.

Table II. - Summary of guideline recommendations

Guideline	Recommendations in trauma patients	
	Pharmacological prophylaxis	**Mechanical prophylaxis**
NICE guideline 92, 2010	NICE recommends LMWH or UFH (for patients with renal failure) if the benefits of VTE risk reduction outweigh the risks of bleeding and where the bleeding risk has been established as low.	NICE recommends use of any one of GCS, foot-pumps or IPC in all patients starting from admission. Advises consideration of temporary IVC filters in very high risk patients where mechanical and pharmacological VTE prophylaxis are contraindicated.
ACCP guideline 8thed. 2008	ACCP recommends that in the absence of a major contraindication, clinicians use LMWH thromboprophylaxis starting as soon as it is considered safe to do so.	ACCP recommends that mechanical thromboprophylaxis with IPC or possibly with GCS alone be used if LMWH is contraindicated. ACCP recommends against the use of IVC filter as thromboprophylaxis.
SIGN guideline 62, 2002	SIGN recommends that LMWH prophylaxis be considered unless contraindicated.	SIGN recommends that mechanical prophylaxis can be considered (e.g. IPC or footpump) in patients with contraindications to LMWH.
EAST guideline updated 2001	EAST advises that LMWH could be used for VTE prophylaxis in trauma patients where these patients do not have other injuries that put them at high risk for bleeding	EAST suggests SCD may have some benefit in spine and head injuries. Foot pumps may be used as a substitute for SCDs where contraindicated due to external fixators or casts. EAST recommends consideration of IVC filters in high risk patients who cannot be anticoagulated

ACCP: American College of Chest Physicians ; EAST : Eastern Association for the Surgery of Trauma (USA) ; GCS : Graduated Compression Stockings ; IPC : Intermittent Pneumatic Compression ; IVC : Inferior Vena Caval Filter ; NICE : National Institute for Clinical Excellence (UK) ; SCD : Sequential Compression Device ; SIGN : Scottish Intercollegiate Guidelines Network ; VTE : Venous Thromboembolism.

Comparisons with other studies

This is the first study to compare thromboprophylaxis guidelines since the publication of new NICE guideline in January 2010. A paper by Struijk-Mulder *et al* (*46*) reviews a number of guidelines of thromboprophylaxis in orthopaedic surgery, and appraises the relevant evidence but does not focus on the trauma patients, who by their vast heterogeneity offer a greater challenge in correctly but safely prescribing thromboprophylaxis.

Implications for practice

All clinicians should recognise the risk of VTE in the trauma patient. Clinicians in the UK should be aware of the recommendations made by NICE as adherence to these guidelines is likely to be closely monitored and strongly encouraged. Meanwhile clinicians in other countries should be aware of local guidelines relevant to their practice and of the commonly cited guidelines internationally. Further work is needed to confirm the hierarchy of efficacy of the various methods of mechanical prophylaxis, the role of multimodal thromboprophylaxis and the potential of oral anticoagulants such as Dabigatrin. Finally following publication of two large studies by Velmahos *et al* questioning the role of all currently used methods of thromboprophylaxis in trauma patients, further work may be required to confirm the efficacy of all of the above methods in a trauma population (*50,52*).

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