Foot and Ankle Surgery xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Foot and Ankle Surgery

journal homepage: www.elsevier.com/locate/fas

Review

Does thromboprophylaxis reduce symptomatic venous thromboembolism in patients with below knee cast treatment for foot and ankle trauma? A systematic review and meta-analysis

Ben A. Hickey [a,*], Ultan Watson [a], Andrew Cleves [a], Raza Alikhan [a], Neil Pugh [a], Len Nokes [b], Anthony Perera [a]

[a] University Hospital of Wales, Heath Park, Cardiff CF14 4XW, Wales, UK
[b] Cardiff University, Cardiff, Wales, UK

ARTICLE INFO

Article history:
Received 18 December 2015
Received in revised form 24 June 2016
Accepted 29 June 2016

Keywords:
Thromboprophylaxis
Deep vein thrombosis
Pulmonary embolism
Low molecular weight heparin
Venous thrombosis

ABSTRACT

Background: Our aim was to determine the evidence for thromboprophylaxis for prevention of symptomatic venous thromboembolism (VTE) in adults with foot or ankle trauma treated with below knee cast or splint. Our secondary aim was to report major bleeding events.
Methods: MEDLINE and EMBASE databases were searched for randomized controlled trials from inception to 1st June 2015.
Results: Seven studies were included. All focused on low molecular weight heparin (LMWH). None found a statistically significant symptomatic DVT reduction individually. At meta-analysis LMWH was protective against symptomatic DVT (OR 0.29, 95% CI 0.09–0.95). Symptomatic pulmonary embolism affected 3/692 (0.43%). None were fatal. 86 patients required LMWH thromboprophylaxis to prevent one symptomatic DVT event. The overall incidence of major bleeding was 1 in 886 (0.11%).
Conclusions: Low molecular weight heparin reduces the incidence of symptomatic VTE in adult patients with foot or ankle trauma treated with below knee cast or splint.

Contents

1. Introduction

Patients with foot and ankle trauma treated with cast or splint immobilization are at risk of venous thromboembolism (VTE) [1]. The most serious complication of this is death from Pulmonary Embolism (PE), which occurs in approximately 1 in 15,000 patients [2]. Although fatal pulmonary embolism is the most serious thromboembolic complication, it is not the only significant adverse event. Approximately 1 in 500 patients will develop a symptomatic PE within 90 days of injury [2]. Many of these patients will be functionally impaired at long term follow up [3]. The other significant complication is symptomatic deep venous thrombosis, which occurs in approximately 1 in 250 patients with non-operatively treated foot and ankle trauma [4]. 20–50% of these patients will develop post thrombotic syndrome [5]. This condition

* Corresponding author at: 10 Trafalgar Road, Penylan, Cardiff CF23 5BQ, Wales, UK.
E-mail address: drhickey@hotmail.co.uk (B.A. Hickey).

http://dx.doi.org/10.1016/j.fas.2016.06.005
1268-7731/

is difficult to treat and therefore it is important to avoid. Considering that lower limb casts and splints are commonly used for a variety of soft tissue and bony traumatic conditions, the population of patients at risk of developing VTE is significant. In view of this, NICE guidelines recommend that patients with foot and ankle trauma and lower limb immobilization should be assessed for risk of development of VTE, and provided with chemical thromboprophylaxis if they have additional risk factors (including cancer, thrombophilia, previous venous thrombosis) [1]. Prophylactic options include either chemical or mechanical methods.

Our aim was to determine the current evidence for the use of chemical or mechanical thromboprophylaxis in the prevention of symptomatic venous thromboembolism in adult patients with foot or ankle trauma treated with below knee cast or splint immobilization. Our secondary aim was to report episodes of major bleeding associated with thromboprophylaxis.

2. Methods

The OVID interface was used to search MEDLINE and EMBASE databases up to 1st June 2015. The following search strategy, previously used by Roberts et al. (2012) was used [6]: (exp venous thrombosis OR exp thromboembolism OR exp pulmonary embolism OR DVT.mp OR deep vein thrombosis.mp OR PE.mp OR pulmonary embolism.mp OR venous thromb$.mp) AND (exp casts surgical OR plaster cast$.mp OR exp immobilization OR immobilization.mp). The search was limited to randomized controlled trials, with no language exclusions. One author performed the study selection based on the following defined inclusion and exclusion criteria. Inclusion criteria: Studies including adult patients of any venous thrombo-embolism risk stratification (including operative and non-operative treatment) with foot or ankle trauma treated with below knee cast or immobilizing splint. Study interventions were chemical or mechanical thromboprophylaxis started within 72 h of injury, with a control group, which had no thromboprophylaxis. The outcomes of efficacy were symptomatic venous thrombo-embolism (pulmonary embolism and deep vein thrombosis) objectively proven with imaging. The outcomes of safety were:

1. Major bleeding i.e. bleeding resulting in death, risk to life or blood transfusion.
2. Clinically important non-major bleed i.e. bleeding that required withdrawal from the study.
3. Minor bleed i.e. any other type of bleed which was not major or clinically important.

Only full papers were reviewed. For trials that reported results in more than 1 publication, data from the most complete publication was extracted and used the other publications to clarify the data. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting of systematic reviews and meta-analyses of randomized clinical trials was followed. Two reviewers performed data extraction independently using standardized data extraction sheets. Discrepancies between the reviewers were reviewed by a third reviewer. Odds ratio and absolute risk reduction for symptomatic DVT were used to calculate number needed to prevent with thrombo-prophylaxis. Mantel Haenszel method was used to assess dichotomous outcomes. Statistical heterogeneity was determined using I^2 statistics. Fixed effects model was used when heterogeneity was <30%, using Review Manager (RevMan 5.0).

The risk of bias for each article was determined by two authors, who independently reviewed the full articles. Data was extracted from articles and a judgement with supporting information was made according the Cochrane Risk of Bias tool. In cases where authors disagreed, the evidence for the judgement was discussed and a consensus opinion was reached. A score from 1 to 3 was given for each of the 7 parameters. Where an item was deemed low risk of bias, a score of 1 was given for the item. A score of 2 was given if the risk of bias was deemed unclear. A score of 3 was given if the item was deemed high risk. The lowest risk of bias score for the 7 items was 7. The highest score was 21. Studies were ranked in decreasing order of risk of bias. Where assessors of outcome were not blinded to intervention group, the study was rated as high risk of bias.

3. Results

Seven prospective randomized controlled trials were included in this review (Table 1). Study details are displayed in Table 2. All of these studies focused on chemical thromboprophylaxis. Only two studies considered patients treated non-operatively [7,8], with all others including patients who underwent surgery. One focused on patients with ankle fractures [9], one focused on Achilles tendon ruptures [10], and the remaining 5 studies include patients with a variety of soft tissue and bony injuries [7,8,11–13]. Included studies did not provide details of numbers of patients with individual risk factors for venous thromboembolism.

The most important additional VTE risk factors for patients with cast immobilization are: lower limb cast immobilization, current hormone replacement therapy/oral contraceptive pill, personal or first degree relative history of VTE, active smoker, any recent hospital admission or major surgery, pregnancy or immediate postpartum, any serious co-morbidity including cardiac failure, chronic obstructive pulmonary disease, chronic renal failure or inflammatory bowel disease, extensive varicosities, active cancer, obesity (BMI >30), known thrombophilia, age >60 years [1]. Considering these risk factors, all of the studies included at least some patients who would be considered at increased risk for VTE (Table 2). In 3 studies, patients were recruited within 72 h of injury [9,13]. Lassen et al. recruited patients within 4 days of injury [12]. In the study by Kock et al., the time to recruitment was not stated, however all patients underwent imaging to exclude DVT prior to entering the study [7]. In two studies, the time between injury and recruitment is not stated [8,11]. It is therefore possible that some patients in these studies may have developed asymptomatic DVT prior to entering the study.

All included studies focused on low molecular weight heparin as the intervention: Subcutaneous Dalteparin 5000 international units once daily [9,13], Subcutaneous Tinzaparin (Innohep) 3500 international units once daily [14], 1750 anti-Xa units of reviparin (Clivarine, Knoll) subcutaneous once daily [12], LMWH (Mono-Embolex) daily s/c injection 32 mg [7], LMWH 36 mg injection once daily [8]. Some of these studies included overweight patients, and without dose adjustment for body weight it is possible that doses may have been sub prophylactic in some patients [7,8].

All chemical thromboprophylaxis studies used venography to confirm asymptomatic DVT, except for the most recent study by Selby et al. [13]. It is important to recognize that technological advances and increased operator experience in the use of non-invasive duplex ultrasonography has made this commonplace. Venography has generally been replaced by ultrasound which is more economical, less invasive and safer [15–17]. In the hands of an experienced operator, ultrasonography has a sensitivity of 100%, specificity of 98% and accuracy of 98% for patients with lower limb DVT when compared with venography [18]. In the most recent study, duplex ultrasound was used to image the lower limb venous system [13].

Please cite this article in press as: Hickey BA, et al. Does thromboprophylaxis reduce symptomatic venous thromboembolism in patients with below knee cast treatment for foot and ankle trauma? A systematic review and meta-analysis. Foot Ankle Surg (2016), http://dx.doi.org/10.1016/j.fas.2016.06.005