Randomized trial

Randomized clinical trial of low molecular weight heparin with thigh-length or knee-length antiembolism stockings for patients undergoing surgery

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Background: **This was a randomized clinical trial to determine the efficacy and safety of a 'blanket' protocol of low molecular weight heparin (LMWH) and the best length of antiembolism stocking, for every patient requiring surgery under general anaesthesia.**

Methods: **Of 426 patients interviewed, 376 agreed to be randomized to receive one of three types of stocking: thigh-length Medi thrombexin® climax™ (Medi UK, Hereford, UK), knee-length thrombexin® climax™ and thigh-length Kendall T.E.D.™ (Tyco Healthcare UK, Redruth, UK). All patients received LMWH thromboprophylaxis. Duplex ultrasonography was used to assess the incidence of postoperative deep vein thrombosis (DVT).**

Results: **No postoperative DVT occurred in 85 patients at low or moderate risk. Nineteen DVTs occurred, all in the 291 high-risk patients: two with the Medi thigh-length stockings, 11 with the Medi knee-length stockings (odds ratio 0·18 (95 per cent confidence interval 0·04 to 0·82); $P = 0·026$) and six with the Kendall T.E.D.™ thigh-length stockings. No patient developed a pulmonary embolism. Stocking groups were similar for age, sex, thromboembolic risk, type of operation and compliance. One significant bleeding complication occurred.**

Conclusion: **A single protocol comprising LMWH and thigh-length stockings abolished DVT in low- and moderate-risk patients, and reduced the rate of DVT to 2 per cent in high-risk patients.**

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Introduction

Currently, the most appropriate means of preventing deep vein thrombosis (DVT) in surgical patients are subcutaneous heparin and antiembolism stockings[1,2], which offer increased benefit when used in combination[3]. Other pharmacological and physical prophylactic methods exist, but are less effective, less safe or impractical[3].

An audit was conducted in this university hospital of the status of thromboprophylaxis to investigate areas for improvement. Of 106 patients who had undergone surgery, heparin prophylaxis was omitted in 43·0 per cent. The use of antiembolism stockings was also disparate and underprescribed to only 46·2 per cent of patients. A variety of stocking brands and lengths was used with inadequate fitting. The combined use of subcutaneous heparin and stockings was evident in only 24·3 per cent of patients. These findings are similar to other reports in the literature describing poor compliance of DVT thromboprophylaxis[4–6].

In order to correct the poor compliance of thromboprophylaxis in the hospital, junior doctors and nurses were tutored in the merits of a single 'blanket' protocol of heparin and stockings for all surgical patients. A repeat audit showed a significant improvement in optimal thromboprophylaxis to 88·1 per cent of patients ($P = 0·003$). The majority of surgical specialties considered low molecular weight heparin (LMWH) to be the best choice for a single-protocol regimen as it is generally more effective[3], more acceptable to patients owing to the single daily injection,

safer and now cheaper than low-dose unfractionated heparin. However, surgeons and nurses remained uncertain about what length and design of antiembolism stocking to apply.

The aim of the study was determine the optimal length of stocking for use in a safe single 'blanket' protocol to prevent postoperative DVT, suitable for all patients at low, moderate or high risk[3] undergoing any surgical procedure performed by a wide range of specialties including breast and oncology, ear, nose and throat (ENT), gastrointestinal, neurosurgery, orthopaedic, urological and vascular surgery. Recent Cochrane reviews gave encouragement for the combined use of subcutaneous heparin and antiembolism stockings[1,2].

The study hypothesis that, provided LMWH is given to all patients, knee-length antiembolism stockings are as effective as thigh-length stockings of the same graduated compression in the prevention of postoperative DVT, was based on the limited evidence in the literature comparing thigh-length with knee-length stockings. The primary endpoint of the study was the rate of postoperative DVT assessed by duplex imaging. A secondary endpoint was the incidence of bleeding complications associated with LMWH.

Patients and methods

A randomized clinical trial was approved by the local Riverside Ethics Committee (London, UK) to compare the efficacy and safety of thigh-length and knee-length antiembolism stockings on a background of LMWH thromboprophylaxis. Patients were interviewed to gain informed consent and for randomization to one of three groups: thigh-length Kendall T.E.D.™ (Tyco Healthcare UK, Redruth, UK), thigh-length Medi thrombexin® climax™ (Medi UK, Hereford, UK) and knee-length Medi thrombexin® climax™ stockings. Randomization was stratified for surgical specialty and thromboembolic risk in line with the international consensus statement for the prevention of venous thromboembolism[3].

The incidence of DVT was assessed by duplex ultrasonography; each patient had preoperative venous duplex imaging on the evening before surgery and a second duplex assessment on postoperative day 5–7. A principal vascular technologist supervised and verified the venous duplex scans.

Stockings were expertly fitted to patients on the evening before the operation, unless the surgical intervention involved the leg; in these patients the stocking was fitted on the first postoperative day.

A single daily subcutaneous injection of 20 mg LMWH, enoxaparin sodium (Clexane®; Aventis Pharma, West Malling, UK), was given to patients on the evening before surgery, except for neurosurgical and orthopaedic patients whose surgeons insisted that they receive the LMWH within 12 h after completion of the operation. Enoxaparin injections were given daily until discharge from hospital.

A record of complications associated with the use of stockings and LMWH was kept. All patients who developed a DVT were treated with full anticoagulation with daily LMWH until adequate warfarinization and class-2 compression hosiery, and were referred for haematological follow-up.

Sample size and statistical analysis

Sample size calculations were based on detecting a possible difference in postoperative DVT rates of 20·0 per cent in the knee-length stocking group and 5·0 per cent in each of the thigh-length stocking groups. These calculations, based on 90·0 per cent power at the 5·0 per cent significance level, required 114 patients per group (342 patients in total).

Statistical analysis was performed using the STATA™ version 6·0 statistical package (Stata Corporation, College Station, Texas, USA). Logistic regression analysis was used to estimate crude odds ratios (ORs) between the three types of stocking. These ORs were also adjusted for the use of preoperative LMWH.

Results

A total of 426 patients were interviewed for entry into the trial; 39 refused and 11 were medically unable to wear antiembolism stockings or to receive subcutaneous LMWH prophylaxis. Three hundred and seventy-six patients were randomized; their mean age was 58 (range 16–88) years and 218 (58·0 per cent) were women. Thromboembolic risk assessment[3] revealed that 291 patients were at high risk, 59 at moderate risk and 26 at low risk. Patients were recruited from a variety of surgical specialties: breast and oncology (73 patients), ENT (13), gastrointestinal (122), neurosurgery (34), orthopaedic (62), urology (58) and vascular venous surgery (14). The patients were randomized into three stocking groups: thigh-length Kendall T.E.D.™ (127 patients), thigh-length Medi thrombexin® climax™ (121) and knee-length Medi thrombexin® climax™ (128) stockings. Randomization was stratified by thromboembolic risk[3] (high, moderate and low) and surgical specialty (breast and oncology, ENT, gastrointestinal, neurosurgery, orthopaedic, urological and

vascular), which produced three similar groups matched for age ($P = 0{\cdot}850$), sex ($P = 0{\cdot}998$), time of commencement of LMWH ($P = 0{\cdot}280$) and thromboembolic risk ($P = 0{\cdot}230$). For each stocking group a statistically similar number of patients did not undergo surgery or postoperative venous duplex imaging ($P = 0{\cdot}277$) (*Fig. 1*).

Trial results

None of the 85 patients at low or moderate risk developed a DVT when this protocol was used. All postoperative DVTs occurred in patients from the high-risk category. Some 19 (6·5 per cent) of 291 high-risk patients developed a DVT; two were bilateral (*Fig. 1*). No patient developed pulmonary embolism during the trial.

The Medi thrombexin® climax™ thigh-length stockings were significantly better at preventing postoperative DVT than the knee-length stockings (two *versus* 11; OR 0·18 (95 per cent confidence interval (c.i.) 0·04 to 0·82); $P = 0{\cdot}026$). Five patients developed unilateral DVT and one a bilateral DVT in the Kendall T.E.D.™ thigh-length group (OR 0·5 (95 per cent c.i. 0·18 to 1·41) *versus* Medi thrombexin® climax™ knee-length stockings; $P = 0{\cdot}190$). Although data for Kendall T.E.D.™ thigh-length stockings were not significantly different from those for either of the other two types of stocking, the results were inconclusive owing to a lack of power between the groups. All the DVTs that developed in patients with thigh-length stockings were found in the calf veins (posterior tibial and peroneal veins). The knee-length stockings were also associated primarily with calf-vein DVT, although one proximal DVT was found in the superficial femoral vein of the thigh.

The patients with postoperative DVT included six having orthopaedic surgery, six gastrointestinal surgery,

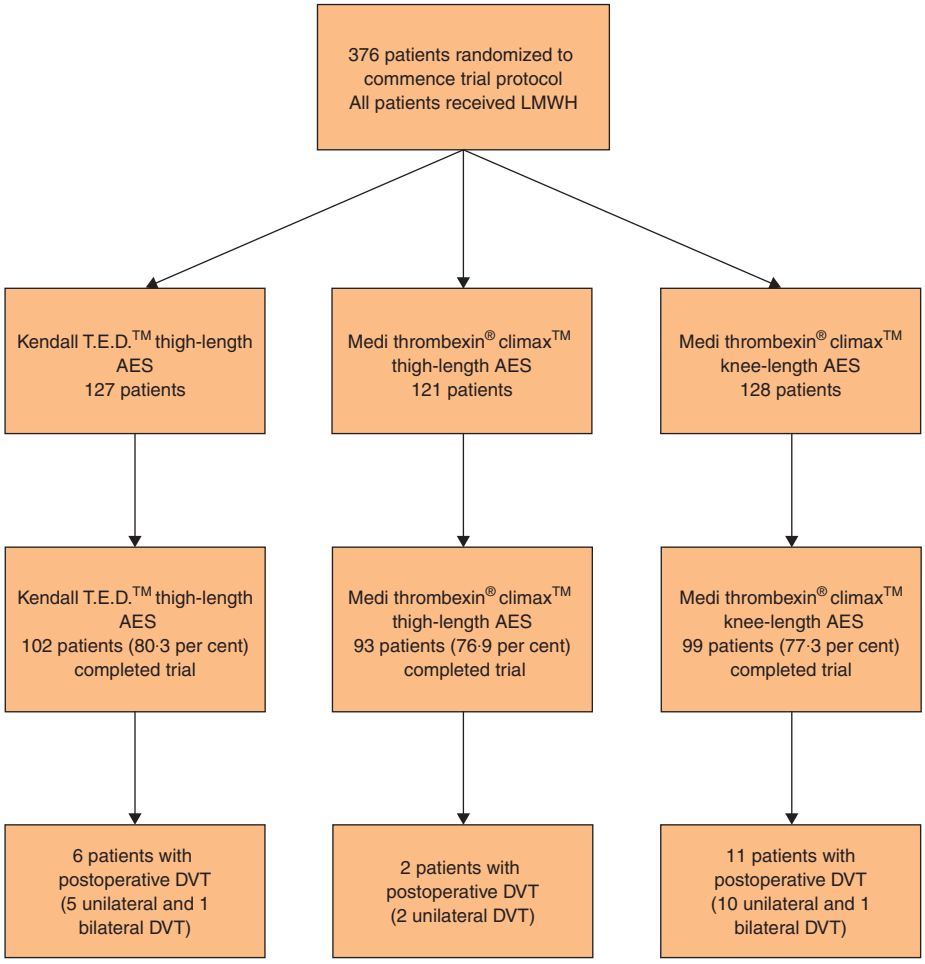

Fig. 1 Trial Consort diagram: patient outcome. LMWH, low molecular weight heparin; AES, antiembolism stockings; DVT, deep vein thrombosis

five urology and two neurosurgery. The DVT occurred with two main types of surgery: 'bone cutting' operations such as hip ($n = 3$) and knee ($n = 2$) replacements, spinal surgery ($n = 2$) and craniotomy ($n = 1$); and major abdominal surgery including upper gastrointestinal operations ($n = 3$), lower gastrointestinal operations ($n = 3$), nephrectomy ($n = 2$), cystectomy ($n = 2$) and prostatectomy ($n = 1$). Of patients undergoing bone-cutting operations, 11 per cent developed a postoperative DVT compared with 5·2 per cent of those undergoing major abdominal surgery; the latter all commenced LMWH prophylaxis before surgery.

The value of preoperative LMWH in reducing the rate of postoperative DVT was investigated by means of logistic regression, which showed similar significance when adjusted for the use of heparin before and after surgery, for the Medi thigh-length *versus* Medi knee-length stockings (OR 0·19 (95 per cent c.i. 0·04 to 0·88); $P = 0·034$) and for Kendall thigh-length *versus* Medi knee-length stockings (OR 0·5 (95 per cent c.i. 0·18 to 1·42); $P = 0·192$). There was weak evidence suggesting that preoperative LMWH was protective in reducing postoperative DVT (OR 0·41 (95 per cent c.i. 0·16 to 1·06); $P = 0·066$). However, this level of significance was diminished when adjusted for randomized groups ($P = 0·110$). Approximately one-half of the patients with postoperative DVT in each stocking group had relevant clinical signs of swelling, tenderness or erythema. Age and malignancy were positive risk factors for DVT; the mean age of the 19 patients with DVT was 68 (range 45–83) years, and 12 of these had a history of malignancy. All patients who developed DVT were treated with full anticoagulation. Warfarin was continued for 6 months under haematological outpatient clinic surveillance.

A record of complications associated with the use of subcutaneous LMWH and antiembolism stockings showed that only one significant bleeding complication occurred; other complications included two minor haematomas that did not require further management, and minor foot abrasions from stockings in three patients. The significant bleeding complication developed when a drain was removed on the second day after parotid surgery; the resulting haematoma required further general anaesthesia for surgical evacuation. The patient made a full recovery.

Discussion

Although numerous investigators have provided evidence to show that prophylaxis against venous thromboembolism is effective in reducing the incidence of DVT and pulmonary embolism by as much as two-thirds, there is still controversy over the correct prophylactic methods and regimens for surgical patients[5]. This uncertainty has frequently led to the inadequate application of thromboembolic prophylaxis in many centres[4–8], despite guidelines in the literature.

A single protocol was deemed appropriate and necessary because findings from previous audits had shown that the majority of surgical patients staying in hospital were at high or moderate risk of thromboembolism. Second, existing protocols prescribe prophylaxis according to risk assessment, which relies on preoperative predictions that may change unexpectedly, such as duration of surgery, postoperative mobility, infection and presence of malignant disease. Antiembolism stockings are effective in the surgical patient, with a reduction in the incidence of postoperative DVT to approximately 11 per cent. Low-dose heparin administered via subcutaneous injection is slightly more effective, reducing the DVT rate to around 9 per cent[3]. In combination, subcutaneous heparin and antiembolism stockings are the most practical and effective prophylaxis in surgery[3,9]. The efficacy, safety and acceptability of these two methods have led to their popularity in surgical practice. It was proposed that LMWH should be given to all patients having surgery under general anaesthesia, except those with medical contraindications. This policy was accepted throughout the surgical specialties, although orthopaedic and neurosurgeons insisted on delayed heparin administration for their patients. The question arose as to which type of stocking was best in combination with LMWH.

Until this trial, only limited evidence was available to distinguish between the benefits of knee- and thigh-length antiembolism stockings. A number of studies have investigated different stockings for effects on venous velocity, patient acceptability and compliance, but only three have compared knee-length with thigh-length stockings for the prevention of postoperative DVT[10–12]. All three studies were randomized, but the number of patients in each was small and none demonstrated a significant difference. A recent review on antiembolic stockings highlighted some of the benefits of knee-length over thigh-length stockings, but offered no evidence on their efficacy in the reduction of postoperative DVT[13]. The international consensus statement[3] refers to the efficacy of knee-length compared with thigh-length stockings in the prevention of DVT as one of the 'key questions to be answered'. The present study showed that thigh-length antiembolism stockings were better at preventing postoperative DVT than knee-length stockings with the same graduated compression profile.

The standard dose of 20 mg enoxaparin was given to all trial patients because it was simple and previous

studies had shown that increasing the dose of LMWH added no prophylactic benefit but increased postoperative bleeding[14].

In this study, orthopaedic and neurosurgeons at least had the reassurance that the major bleeding problems they feared did not occur. For them to allow LMWH to be given 12 h before surgery could have increased the rate of bleeding whilst lowering the DVT rate. Patients undergoing 'bone cutting' or abdominal surgery are at high risk of thromboembolic complications and therefore require optimal prophylaxis. In the present study, neurosurgical and orthopaedic patients who received only postoperative LMWH had the highest rate of postoperative DVT, approximately twice that of the other specialties where LMWH was given before the operation. The surgical procedure initiates the thromboembolic process and therefore starting the heparin prophylaxis before surgery is probably optimal, although further research in this area is required. LMWH commenced the evening before operation also permits the use of epidural or spinal anaesthesia at the time of surgery.

The combination of a good-quality thigh-length stocking and LMWH for patients undergoing surgery produced a postoperative DVT rate of 2 per cent in high-risk patients and zero in patients at moderate or low risk. This simple and safe protocol for DVT prophylaxis of LMWH and antiembolism stockings can be given to all surgical inpatients. To have a single hospital protocol means that prophylaxis against DVT is less likely to be forgotten. If a specialty insists on a delay in administration or an increased dosage for certain patients, this can be accommodated. Patients with medical contraindications to LMWH or stockings could receive only appropriate prophylaxis.

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