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Intermittent pneumatic compression reduces the risk of deep vein thrombosis during post-operative lower limb immobilisation

A prospective randomised trial of acute Achilles tendon ruptures

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Abstract

Deep vein thrombosis is a common complication when immobilising the lower limb after surgery. We hypothesised that adjuvant intermittent pneumatic compression (IPC) during post-operative outpatient immobilisation of the lower limb could reduce the incidence of deep vein thrombosis (DVT).

A total of 150 patients with acute Achilles tendon rupture were randomised to either treatment with IPC for six hours daily ($n = 74$) under an orthosis or treatment as usual ($n = 74$) in a plaster cast. At two weeks post-operatively the incidence of DVT was assessed using compression duplex ultrasound (CDU) by two ultrasonographers blinded to treatment. After the IPC intervention had ended, all patients were immobilised in the orthosis for another four weeks and a second CDU was performed.

Trial registration: www.clinicaltrials.gov; NCT01317160.

At two weeks the DVT rate was 21% in the IPC group and 38% in the control group (OR = 2.36; 95% CI 1.11 to 5.01). Age > 39 years was found to be a strong risk factor for DVT (OR = 4.84; 95% CI 2.14 to 10.96). Treatment with IPC corrected for age reduced the risk significantly (OR = 0.36; 95% CI 0.16 to 0.80). At six weeks, however, the frequency of DVT was 49% in the IPC group and 51% in the control group (OR = 0.94; 95% CI 0.49 to 1.83).

IPC seems to be an effective method of reducing the risk of early DVT in leg-immobilised outpatients. A high risk of DVT during prolonged immobilisation warrants further study.

Introduction

Trauma and surgery requiring lower limb immobilisation are commonly associated with potentially preventable complications such as deep-vein thrombosis (DVT) and/or pulmonary embolism (PE), also named venous thromboembolism (VTE) (1-3). Without prophylaxis, immobilisation of the lower extremity is associated with an estimated VTE rate of 20% (4, 5). Patients immobilised in plaster cast after Achilles tendon rupture (ATR) are at especially high risk; the VTE incidence being 36-50%, irrespective of operation or conservative treatment (6-8). Hence, DVT preventive interventions during lower limb immobilisation are, although debatable (9), often recommended (5).

Low molecular weight heparin (LMWH) in lower limb immobilised patients, has in systematic reviews shown to give a small reduction of VTE, the incidence being 0-37% versus 4.3-40% without prophylaxis (5). However, a randomised controlled study on 105 patients immobilised in plaster cast after ATR surgery demonstrated no effect of LMWH (6). The DVT incidence was 34% in the thromboprophylaxis group (Dalteparin 5,000 U daily, 6 weeks) and 36% in the control group ($p=0.8$). Thus, albeit pharmacological prophylaxis is frequently recommended, it does not seem effective in reducing DVT incidence during limb immobilisation (9). Scarce blood circulation associated with immobilisation may be one explanation.

One approach to increase blood flow and to prevent DVT during limb immobilisation is to apply mechanical intermittent pneumatic compression (IPC) therapy (10-12). Systematic reviews have demonstrated reductions in DVT when adjuvant treatment with IPC is applied after hip- and knee replacement surgery in hospitalized patients (13, 14). Whether IPC

treatment applied during lower limb immobilisation and performed in an outpatient setting can reduce the incidence of DVT is unknown.

The primary aim of this randomised, controlled trial was to assess the efficacy of two weeks of mechanical calf IPC intervention beneath an orthosis to reduce the DVT incidence after ATR surgery compared to treatment-as-usual with plaster cast. The secondary aim was to investigate the DVT-incidence after cessation of the IPC intervention, i.e. at 6 weeks, when both groups had exhibited continued orthosis immobilisation.

Materials and Methods

Patients: This prospective randomised study (www.clinicaltrials.gov; trial number NCT01317160) was conducted with approval by the Regional Ethical Review Committee in Stockholm, Sweden. Verbal and written information consent about the trial was received by all eligible subjects. The inclusion criteria included: acute unilateral ATR, operated on within 96 hours, and age between 18 and 75 years. The exclusion criteria were: inability to give informed consent; current anticoagulation treatment (including high dose acetylsalicylic acid); planned follow-up at other hospital; inability to follow instructions; known kidney failure; heart failure with pitting oedema; thrombophlebitis; thromboembolic event during the previous three months; other surgery during the previous month; known malignancy; haemophilia; and pregnancy.

Between March 2011 and June 2013, 389 patients with ATR were screened for eligibility at the Karolinska University Hospital and Södersjukhuset, Stockholm (Figure 1). One hundred-fifty patients (126 men and 24 women) at a mean age of 40 years (range 18-71) were included, and operated at the Karolinska University Hospital, Stockholm. Patients were enrolled and assigned to the interventions either by a third party nurse or by a research nurse. Randomisation was performed with use of computer-generated random numbers in permuted blocks of four, through an independent software specialist, and consecutively numbered, sealed, opaque envelopes opened after surgery and prior to treatment. The patients were randomised to undergo either standard plaster cast treatment alone or calf IPC beneath an orthotic device. Since a prior study demonstrated that IPC application under plaster cast was not feasible the intervention group received calf IPC under an orthosis (8).

Two patients were initially included, one in each group, in the study despite one patient having an ongoing thrombosis and the other being too young and therefore they were excluded from the study directly after randomisation.

Eight patients, five in the IPC group and three in the control group, interrupted their participation before follow-up (Figure 1). This was due to unwillingness to continue within the research project (n=4), violations of the research protocol (n=2), difficulties to tolerate the IPC device (n=2). The number of patients analysed in the intention-to-treat analysis (ITT), i.e. all randomized patients, was in the treatment group sixty-nine (n=69) and in the control group seventy-one (n=71) (Figure 1). Non-acceptable compliance was set to <10 hours of IPC usage, and, thus, two patients were withdrawn in the per protocol analysis (PP). Hence, the number of patients in the PP analysis was in the treatment group sixty-seven (n=67) and in the control group seventy-one (n=71)

Surgical procedure: After administration of 20 ml of local anaesthetic (Marcain 5 mg/ml with adrenaline), without the use of a tourniquet, a longitudinal 5-10 cm dorsomedial skin incision was made. The paratenon was incised on the midline. The tendon stumps were end-to-end sutured using modified Kessler suture technique with two 1-0 polydioxanone (PDS II) sutures. Thereafter, the paratenon and fascia cruris were separately sutured using 3-0 Vicryl, and the skin was closed with 3-0 Ethilon. All sutures were supplied by Ethicon, Somerville, NJ, USA.

Post-operative treatment protocol: Patients in the IPC group received two weeks of six hours daily bilateral calf IPC (Venaflo® Elite, DJO LLC, Vista, CA, USA) applied under an orthosis with 3 wedges (Aircast® XP Walker™, DJO LLC, Vista, CA, USA) and were allowed to weight-bear as tolerated (Figure 2). As the IPC-device cycles, the distal chamber inflates to

73 mm Hg over a 0.5-second period. During the last 0.2 second of this period, the proximal chamber inflates to 63 mmHg and then settles at 45 mm Hg. After six seconds of inflation the cuff deflates, and the cycle is repeated every minute. The patients were instructed to apply the intermittent pneumatic compression therapy during the time they were sedentary, i.e. sitting or lying in bed sleeping, 6 hours at a minimum daily. Patient compliance was registered by the patient and by the device. Intermittent pneumatic compression treatment was discontinued two weeks post-operatively.

The patients of the control group received treatment-as-usual, i.e. a below-knee plaster cast with the ankle in 30 degrees equinus position in the outpatient clinic shortly after the completion of surgery, and were non-weight-bearing with crutches during the first two weeks.

All patients were prescribed paracetamol 500 mg / codeine 30 mg to cope with the post-operative pain. No pharmacological anti-inflammatory or thromboprophylactic drugs were given to the patients post-operatively.

At the two-week visit all patients received a lower leg orthosis (Don-Joy Walker; DJO, Vista, California) and were instructed to start full weight-bearing. The orthotic treatment was stopped at six weeks post-operatively.

Assessment of deep venous thrombosis (DVT): At 2 and 6 weeks post-operatively, all patients were screened for DVT in the operated leg by unilateral compression duplex ultrasound (CDU). Two experienced ultrasonographers, blinded to the treatment regimens, performed all the CDU using a Philips CX 50 ultrasound machine (Philips Medical Systems, Andover, MA, USA). The standard procedure included evaluation of all deep proximal and distal veins, including muscle veins, as well as vena saphena magna. The criteria for DVT

diagnosis and the diagnostic procedure have been described earlier (15). Proximal DVT was defined as a thrombosis that involved the popliteal vein or any more proximal veins, with or without involvement of the calf veins. Briefly, the DVT diagnosis was based on a transversal ultrasound compression test of the blood vessel, and assessment of blood flow in the veins by color Doppler flow.

The compression duplex ultrasound scans performed at two or six weeks denoting a DVT were re-evaluated after completion of the study, by analysing the CDU film sequences. The second assessment was performed by another ultrasonographer blinded to the treatment allocation. This *post hoc* examination verified the first diagnosis by demonstrating DVTs in the same anatomical localizations as the initial analysis.

Other demographic data: Variables including age, gender, body mass index (BMI), smoking habits, time to surgery, time in surgery, and the duration of daily intermittent pneumatic compression were registered for each patient.

Other assessments: The patients in this study also underwent functional testing and were assessed with patient-reported outcome. These assessments, however, are still ongoing and will be reported separately.

Statistical analysis: Our and other recent studies showed the rate of CDU verified DVT after ATR surgery to be 40 % (6-8). Based on earlier studies of IPC, and our own pilot study, we estimated a 60% risk reduction of the incidence of DVT(17). Thus, fifty-four patients per group would be required to detect a difference of 24% in the DVT rate (two-sided type-I error rate = 5%; power = 80%).

All variables were summarized with standard descriptive statistics such as mean, standard deviation, and frequency using SPSS v19.0 software (SPSS Inc., Chicago, Illinois).

Categorical variables, e.g. differences between the IPC- and control group in occurrence of DVT, were analyzed with Pearson's χ^2 -test or Fisher's exact test if one cell had an expected cell count less than 5. Differences in continuous variables, such as age and time to surgery, were scrutinized for severe skewed distributions or outliers. However, no such distributions were found and, thus, these variables were analyzed with Student's t-test. The level of significance was set to less or equal to 0.05 (two-tailed).

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Results

Patient characteristics

There were no significant differences in age, sex, smoking habits, BMI, time to surgery, and time in surgery between the IPC treated patients and the controls (Table I). The treated patients exhibited a mean of 70.3 hours (range 2.25-182.5) in the ITT analysis and 71.3 hours (range 18.1-178.5) in the PP analysis of self registered application of IPC. The self-registered application of IPC correlated well with the device registered usage of 67.3hours (range 0.73-178.5) in the ITT analysis and 71.3 hours (range 40.0-178.5) in the PP analysis.

DVT incidence during IPC intervention

Screening with CDU at two weeks post-operatively demonstrated a DVT in 23% (n= 16/69) in the ITT analysis and 21 % (n=14/67) in the PP analysis of the patients in the IPC group and in 37% (n= 26/71) patients in the control group (Table 2). The patients compliant with the IPC-treatment exhibited a significant reduction in the risk of DVT, after correction for age differences between groups (ITT analysis: OR= 2.11; 95% C. I. = 0.97-4.62; p=0.061 and PP analysis: OR=2.60; 95% C.I. 1.15-5.91; p=0.022) (Table 2). No proximal DVTs were detected and no clinical PEs were diagnosed.

DVT incidence after cessation of IPC intervention

After ending the IPC intervention and subsequent orthosis immobilisation in both groups, screening at six weeks post-operatively using CDU showed a DVT in 52% (n= 36/69) of the patients in the IPC group and in 48% of (n= 34/71) the patients in the control group (OR= 0.94; 95 % C.I. 0.49-1.83). One proximal DVT was detected in the control group. The patient

had a DVT in vena fibularis at 2 weeks and was treated with LMWH but still had a progression of the DVT. No clinical signs of PE were observed in any of the patients.

Other post-operative complications

At two weeks post-operatively there were no wound infections seen. Six wound infections were observed at six weeks post-operatively, two in the IPC group (3.0%) and four in the control group (5.5%; Fisher's exact test= 0.682). The infections were treated with isoxazolympenicillin (5) or clindamycin (1) and healed successfully. We observed two re-ruptures due to new trauma, one from each group. The patients were successfully re-operated but excluded from further examination within the study.

Discussion

This prospective randomised study demonstrated that compliant usage of adjuvant calf IPC, patient administered in an outpatient setting, produced a significant reduction of distal DVTs after two weeks of post-operative lower limb immobilisation as applied to Achilles tendon rupture (ATR) patients.

The frequency of DVT in the control group (37%) found in this study is in agreement with previously reported, 36%, in other randomized controlled studies on CDU verified DVT after surgical treatment of acute ATR (6-8). The characteristics of the patient population in this study did not differ from that of the three earlier studies reporting on DVT rates after ATR surgery (7, 8, 16). Half of the patients in this study, however, received adjuvant calf IPC applied under an orthosis, which has not been applied in other studies. The reduced DVT incidence in the compression treatment group indicates that the IPC therapy may prevent the development of DVT during immobilisation.

From the current study, we cannot fully discriminate to what degree the DVT preventive effect is related to calf IPC or to orthosis mobilisation, respectively. However, our data at six weeks, showing increased number of DVTs in the treatment group after the IPC intervention was concluded and all patients were treated with orthosis mobilisation, suggest that the major DVT preventive effect is related to the IPC therapy. The study does not, however, allow any conclusion as to the preventive effect of IPC in a long-term perspective, such as six weeks.

The reduction in DVT observed at two weeks in the IPC compliant group is probably related to reduced venous stasis produced by the intermittent mechanical calf compression. IPC has thus been shown to increase venous peak flow velocity by > 200%. (12)

The decreased incidence of DVT may also be related to effects on intrinsic fibrinolysis observed after IPC. Hence, cyclical tissue shear stress induces the production of chemical substances: antithrombotic tissue factor pathway inhibitor and pro-fibrinolytic substance tissue plasminogen activator. (12)

The increased blood flow caused by IPC may additionally have a positive effect on fracture and soft tissue healing during immobilisation. (12, 21, 22) Although immobilisation significantly impairs healing, experimental IPC applied under a plaster cast has been shown to promote healing by activating chemical substances that are known to enhance tissue repair. (12, 21, 22) Thus, further studies of the efficacy of compression treatment on tissue healing and functional outcome after immobilisation are needed. Recording of functional- and patient-reported outcome from this study is ongoing and will be presented separately.

To our knowledge this is the first study examining the effects of IPC in an outpatient setting. However, compliance with IPC therapy has been raised as an issue that could be even more debatable in the outpatient setting (13, 17). The intention-to-treat analysis demonstrated a trend toward significance, while the per-protocol treatment efficacy was significant. These findings reflect that IPC therapy is effective only while using it and that compliance is an important issue. Eisele et al. have shown that fewer than six hours of IPC treatment per day led to more DVTs than IPC treatment exceeding six hours per day (17). Thus, the patients in this study received instructions to use the IPC device for at least six hours per day, to which the patient- and the device-registered data demonstrated fairly good adherence.

After the end of the IPC intervention at week two, the DVT incidence at six weeks post-operatively was similar in the two groups, around 50%. This suggests that the

DVT preventive effect of the IPC therapy does not persist after cessation of treatment when continued immobilisation is applied. Therefore, the DVT frequency at six weeks additionally indicates that the IPC therapy should be scientifically studied during the whole time of post-operative lower limb immobilisation.

Moreover, the observed 50 % DVT incidence at six weeks of orthosis mobilisation with weight-bearing suggests that the recommendation of immediate weight-bearing and mobilisation in an orthosis is not enough to prevent the development of DVT. This seems to confirm that significant reduction in mobility in itself, although weight-bearing in an orthosis, is a risk factor for development of distal DVTs. Yet, the clinical significance of distal DVTs is debated, but guidelines from different countries give diverse recommendations. Some advice LMWH treatment to all leg immobilised patients, while most guidelines recommend assessment of risk factors for VTE [nice]. Thus, risk assessment is an essential clinical tool for identifying those patients in need of prophylaxis [nice].

The correlation analysis of risk factors demonstrated that leg-immobilised patients aged > 39 years exhibited an almost fivefold increased risk of DVT. Other risk factors, such as BMI, smoking, time to and time in surgery, did not significantly affect the risk of DVT in this study. Increased age is therefore a strong risk factor, as is also stated in many guidelines, e.g. by NICE, UK [NICE]. This study therefore suggests that patients aged > 39 years, which are leg immobilised after ATR surgery could be considered for prophylactic measures against DVT.

The detection of calf DVT with CDU is technically challenging, but the results demonstrating that half of the patients experienced a DVT at six weeks are in line with recent studies. (8,18) Our methodology also included experienced ultrasonographers who were blinded to the treatment regimens. Moreover, positive findings of DVT were re-evaluated

after completion of the study. This re-evaluation demonstrated no difference between the assessments, which corroborates the findings of this study.

Earlier studies have shown that assessment of symptomatic DVTs in ATR patients is not possible, owing to difficulties in differentiating symptoms of DVT from normal post-operative findings. (6) Therefore this study did not assess the number of symptomatic DVTs. One proximal DVT was detected in a patient treated with plaster cast, but no clinical signs of PE were observed, which is in accordance with earlier studies showing a low incidence of clinical PE after ATR. (6) However, PE after lower limb immobilisation does exist, and even fatal PE may occur. (19, 20) Further studies should examine the IPC preventive effects on proximal DVTs and PEs on large patient populations.

The reduction in DVT risk (37% vs. 21%) seen when using mechanical IPC prophylaxis suggests an advantage over pharmacological prophylaxis. Previous randomised controlled studies on LMWH during lower limb immobilisation mostly demonstrated a non-significant DVT preventive effect, (6) therefore CHEST guidelines do not recommend pharmacological thromboprophylaxis in patients with isolated lower-limb injuries requiring leg immobilisation. (9) Presumably, scarce blood circulation in the immobilised lower limb leads to a decreased local LMWH concentration and a non-significant effect. Mechanical prophylaxis, on the other hand, addresses the problem of stasis and may serve as a targeted therapy.

Whether mechanical prophylaxis should be administered as an outpatient treatment for leg-immobilised patients at risk for DVT is also a matter of cost-benefit analysis, which was not possible in this study. Earlier investigations demonstrated no DVT-preventive effect with LMWH in ATR patients. (6) This study, however, established IPC

prophylaxis as a feasible and efficient treatment alternative, at least during early immobilisation.

In summary, patients with post-operative lower limb immobilisation after ATR demonstrate significantly reduced rates of distal DVTs when using adjuvant calf IPC for two weeks. Moreover, orthosis immobilisation at six weeks post-operatively is still associated with a high number of DVTs. This study of post-operative lower limb-immobilised patients implies that mechanical IPC treatment may be a viable and effective prophylactic treatment against DVT, also in an outpatient setting.

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