STOP Leg Clots
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Swedish-international multicenter Trial of Outpatient Prevention of Leg Clots

Prevention of thromboembolism and failed healing during lower limb immobilization – a multicenter study with adjuvant intermittent pneumatic compression therapy

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Purpose and Aims

Complications related to lower limb immobilization, such as venous thromboembolism (VTE) and delayed healing, after musculoskeletal trauma and reconstructive surgery represent increasing problems. The National Health Service in England has identified prophylaxis of VTE as the number one prioritized intervention [1 2].

As a result of trauma and post-operative lower limb immobilization and associated impaired neuro-vascular supply, patients exhibit an increased risk of VTE and hampered healing. Pharmacoprophylaxis for VTE in patients with lower-leg immobilization has, however, demonstrated low or non-effectiveness[3 4 5]. Thus, there is no consensus for prevention, and a need for novel treatment strategies [1 2 4].

Our hypothesis is that leg immobilization calls for promoted blood circulation using adjuvant mechanical compression. This intervention, in the form of intermittent pneumatic compression (IPC) therapy, targets the primary cause of impaired neuro-vascular flow. IPC might reduce the risk of VTE and improve healing by respectively increasing the local supply of anticoagulants and healing mediators.

We aim to demonstrate that adjuvant, outpatient IPC-therapy in lower-leg immobilized patients, compared to treatment-as-usual, reduces VTE-incidence and improves healing. This VTE-preventive intervention can without delay be adapted in daily health care in order to increase patient safety and reduce costs as compared to pharmacological alternatives.

The primary outcome measure is the VTE-incidence at the end of immobilization, i.e. about at six weeks. Secondary outcome measures are patient-reported outcome assessed with validated scores, and effects on healing callus production with microdialysis and levels of profibrinolysis factors.

Survey of the Field

International guidelines offer opposing recommendations regarding VTE-prevention during leg-immobilization. The American College of Chest Physicians recommends no pharmacologic thromboprophylaxis, low molecular weight heparin (LMWH), due to the increased risk of bleeding in relation to the expected low effect of LMWH[4]. Furthermore, NICE, UK, recommends to consider offering LMHW to leg-immobilized patients after evaluating the risks of VTE and bleeding[1]. Thus, today the clinical practice of VTE prevention in leg-immobilization varies considerably [6 7], and lacks strong evidence[5].

The risk of VTE in association with trauma/surgery and leg-immobilization is high, with an estimated deep venous thrombosis (DVT) rate of 25% up to 50% after e.g. Achilles tendon rupture (ATR)[8 9]. Today it is known that also asymptomatic DVTs often may result in pulmonary embolism[10]. Pharmacologic thromboprophylaxis (LMWH) in patients with lower-

leg immobilization has, however, shown to be low- or even non-effective in some studies[5 7 3 4 11]. The latest meta-analysis of LMWH in leg-immobilized patients show only a moderate prevention on DVT because risk of bias and no preventive effect on pulmonary embolism[5]. Moreover, LMWH exerts adverse effects on the healing process[12] and increases the risk of bleeding complications[3 4]. Thus, NHS, UK and SBU, Sweden have identified the need to develop safer and more efficient VTE-prophylaxis[1 2 13].

Mechanical thromboprophylaxis (IPC) reduces VTE, is a cost-effective intervention in hospitalized patients, and is recommended by guidelines for surgical patients[1 14]. Whether IPC treatment applied during leg immobilization and performed in an outpatient setting can reduce the incidence of DVT is unknown. Therefore, mechanical thromboprophylaxis is not yet mentioned in guidelines for leg-immobilized patients. Recently, however, we published the first evidence that leg immobilized patients with ATR treated with adjuvant IPC exhibited a DVT-rate of 21% compared to 37% in the controls at 2 weeks. IPC intervention ended at two weeks, and thus at 6 weeks the DVT-rate was 50% in both groups[9].

Thus, it remains to show if prolonged adjuvant IPC therapy during the whole 6 weeks immobilization period could reduce the incidence of VTE in leg-immobilized patients, also in patients with fractures. Can the IPC treatment synchronously enhance the healing process so that it will lead to a long-term increased patient-reported outcome? Recent studies suggest that the increased neuro-vascular flow induced by IPC enhances the healing process[15].

Research question

The primary research question is:

- Does addition of IPC to patients with lower limb immobilization in routine care, reduce the incidence of VTE up to the end of immobilization, i.e. 6-8 weeks.

Secondary questions are:

- Can adjuvant IPC during leg immobilization enhance fracture/soft tissue healing and improve patient-reported outcome?
- Does IPC reduce VTE incidence by upregulation of profibrinolysis?

Variables and measures

Primary outcome (binary), VTE, is defined as symptomatic or asymptomatic deep venous thrombosis (DVT) assessed at six weeks of immobilization by screening compression duplex ultrasound (CDU), or symptomatic pulmonary embolism detected by computer tomography. Assessors of CDU will be skilled ultrasonographists, masked to the treatment allocation[9]. The CDU-examination will document absence/presence of thrombus in the calf, popliteal and femoral veins separately, as previously described[9]. All positive examinations and those considered technically difficult will be reviewed by a specially trained vascular physician (blinded to the treatment allocation), who will establish the diagnosis and classify the examination result as absence or presence of thrombus. This will show the incidence of VTE in each group.

We acknowledge that the CDU assessment of DVT will be the dependent measure of outcome since DVT is more common than pulmonary embolism. CDU screening (surrogate outcome), can be justified because of the clinical significance attributed to even asymptomatic DVTs, which today are known to cause a high rate of pulmonary embolism, affect the patient outcome[16] and are treated by most clinicians with anticoagulant therapy[10]. To reliably confirm or refute an effect of IPC on survival or clinical pulmonary embolism a

randomized trial would require a sample size of several tens of thousands of patients; this is not currently possible.

The secondary outcome measure is patient-reported outcome (PRO) assessed with reliable and validated rating-scales (0-100 points); EuroQol (EQ-5D-5L), the Achilles Tendon total Rupture Score (ATRS), foot and ankle outcome score (FAOS), and Olerud-Molander Ankle Score (OMAS) at 6 and 12 months. Data of both groups (IPC vs. no IPC) will be presented by mean, median, standard deviation, and range. EQ-5D-5L is a validated, generic health-related quality of life measure consisting of five items each with a five-level answer possibility. Each combination of answers is converted into a health index score[17]. The EQ5D-index is measured on an interval scale and, thus, analyzed with parametrical statistics. ATRS (ordinal scale) is a validated ATR PRO measure[18], while OMAS (ordinal scale) and FAOS (ratio scale) are validated for ankle fractures[19]. Functional evaluation of the ATR-healing will be performed by the validated heel-rise test at one year post-injury[18 16]. Heel-rise height and work (continuous data) of both groups will be presented[20].

Callus production (continuous data) in ATR and ankle fracture (AF) patients will be assessed at six weeks using microdialysis followed by quantification of procollagens, which recently emerged as a method to assess tendon healing[15 22 23]. For fracture healing quantification of bone formation markers (alkaline phosphatase, osteocalcin, and pro-collagen type I propeptide) will be performed.

VTE-preventive mechanisms will be analyzed at the six week visit by assessments of profibrinolysis and coagulation as well as by blood-flow quantification using ultrasound[24]. Overall hemostatic potential (OHP), D-dimer, plasminogen activator inhibitor-1 (PAI-1), endogen trombin potential, trombin antitrombin complex, plasmin antiplasmin complex, tissue plasminogen activator/PAI complex will be assessed at Karolinska Institutet, Coag. Unit, Ass. Prof. J. Antovic. Peak femoral blood velocity will be calculated using custom ultrasound software and compared with baseline values, while microcirculation and tissue oxygenation will be assessed by near-infrared spectroscopy (INVOS®)[25 24]. These explanatory continuous data will be compared between the groups.

Further patient data that will be analyzed as secondary outcome measures at 2 and 6 weeks are adherence to allocated treatment and adverse events related to IPC. Adverse events (binary) that will be registered are 1) Any damage to the skin of the legs including infection. 2) Any reasons for prematurely stopping the IPC. 3) Any fall associated with significant injury occurring within 6 weeks of enrollment. The frequency of the adverse events of each group will be presented[9].

Health economic analyses, together with Karolinska Institutet, LIME, Med. dr. Peter Lindgren, of the trial treatment effects will involve a within-trial evaluation of cost effectiveness integrated into a decision-analytic model of longer run costs and health effects.

Study Design (PICO)

“STOP leg clots” is an international, multicentre prospective randomized, controlled, parallel group trial with blinded assessment of the outcome. The allocation ratio is 1:1. The study has an Ethical review board approval 2016/1753-31 and is registered at clinicaltrials.gov.

Patients: At least 20 hospitals in a minimum of twelve regions have accepted to participate, and this captures a study population, which is representative of Sweden. The included patients, ATR and ankle fractures, are representative of, and constitute a large part of the population with lower limb immobilization. Moreover, patients with ATR and AF have

demonstrated low- or non-effectiveness of LMHW prophylaxis also in relation to the risk of bleeding complications[3] [4]. Therefore, there is a need for an alternative prophylaxis with documented effects.

In the perspective that different hospitals have different clinical traditions/indications for surgery of ATR and AF we have chosen to include both operated and non-operated ATR/AF, since both groups are equally served by VTE prophylaxis. Earlier studies have shown a just as high incidence of VTE in non-operated as in operated ATR/AF [6], further indicating a benefit of demonstrating a VTE risk reduction in both operated/non-operated lower limb immobilized patients. Surgery vs. no surgery will be accounted for in the statistical analysis.

Intervention: There is a need for new VTE prophylactic methods, especially in lower limb immobilized patients. IPC has been demonstrated cost effective both as adjuvant and versus no pharmacoprophylaxis in hospitalized patients by NICE. However, in an outpatient setting there are yet only recent short-term data of the efficacy of IPC. There is a need for data on the efficacy of IPC during long-term leg immobilization to inform guidelines.

The intervention, *addition of IPC to routine care*, will be administered in the emergency department or in the outpatient clinic. Patients will during the six weeks of lower limb immobilization receive bilateral calf IPC (Venaflow Elite, DJO LLC, Vista, CA, USA) applied under an orthosis (Aircast® AirSelect Elite, DJO LLC, Vista, CA, USA). This IPC-system delivers rapid inflation and graduated sequential compression. The IPC device is mobile and should therefore not restrict patient mobilization, but can be taken off if the patient wants to mobilize independently. The patients will be instructed to apply the IPC-therapy continuously, both day and night. Compliance with the treatment will be registered by both the patient and by the device[9]. American College of Chest Physicians recommend that efforts should be made to achieve 18 h of daily compliance with IPC in hospitalized patients[17]. However, there are no recommendations for mobile outpatients. Outpatients were in our recent study recommended at least 6h daily therapy, and in this study we will increase the recommendation to 10h/daily. Graduated compression stockings are part of IPC-care and these should be applied and worn under the IPC sleeves on both legs. IPC will be discontinued if the patient declines to continue IPC or had adverse effects of the IPC that warrants removal. At the 2 and 6 weeks visit the orthosis will be removed by a nurse and the patient will be examined by an orthopaedic surgeon (masked to the treatment allocation), who will document compliance and adverse events. At the 6 weeks visit the patient will also be sent for CDU-examination, which will document the main outcome. Patients will during the six weeks leg immobilization be weight-bearing with crutches or non-weight-bearing with crutches according to the preference of the orthopedic surgeon (masked to the treatment allocation). Weight-bearing will be recorded and accounted for in the statistical analysis.

Comparator: Since there are no documented highly effective therapies for DVT reduction during leg immobilization, and guidelines vary regarding prophylaxis, we chose to use treatment-as-usual as a comparator, regardless of LMHW use or not[3] [4]. Based on our calculations less 10% of the patients will receive LMHW in clinical practice and our power calculations has taken this into account. NICE has stated that LMWH is not a feasible general treatment, especially health economically, during six weeks for all patients with leg immobilization. One review, including 1,490 patients from six randomized trials, showed a small reduction in DVTs using LMHW[8]. However, they concluded that more research is needed to develop more effective and safe thromboprophylactic treatments. Moreover, since a study with LMHW as a comparator would necessitate too many patients - this was not an option. The main research question remains: Is adjuvant IPC more effective than routine care for reducing the incidence of VTE in patients during lower limb immobilization? The usage of no general VTE-prevention in the comparator group is moreover justified since a DVT-screening will be performed on all patients. LMWH vs. no LMWH will be accounted for in the statistical analysis. If a VTE is detected we will follow clinical guidelines and initiate

pharmacological VTE-treatment.

The comparator**, routine care,** lower limb immobilization will be administered by normal routine in the emergency department or in the outpatient clinic. Routine care include that the lower limb will be immobilized in an orthosis or a below-knee plaster cast according to local routines. At the 2 and 6 weeks visit the orthosis/plaster cast will be removed by a nurse who will document compliance. Subsequently, the patient will be examined by an orthopaedic surgeon (masked to the treatment allocation), who will document adverse events. At the 6-8 weeks visit the patient will also be sent for CDU-examination, which will document the main outcome. Patients will during the six weeks leg immobilization be weight-bearing with crutches or non-weight-bearing with crutches according to the preference of the orthopedic surgeon (blinded to the treatment group). Weight-bearing will be recorded and accounted for in the statistical analysis.

Outcome: The primary outcome, VTE at 6 weeks post-immobilization, will best be assessed by screening CDU of DVTs. CDU is rapidly becoming the investigation of choice to confirm the diagnosis of DVT since it is non invasive. It is acceptable to patients, can easily be repeated several times and uses equipment, which is widely available. Thus consent, accrual and adherence in a trial are likely to be more easily achieved than with alternatives.

The primary outcome will be validated by the explanatory outcome of VTE-prevention, assessed by quantification of blood flow, profibrinolysis and coagulation factors from blood serum taken by a study nurse at the 6 weeks visit.

A long-term effect of IPC on VTE and healing will be confirmed by the secondary patient-reported outcome measures (PROM). We have data suggesting that an asymptomatic DVT affects PROM at 1 year[16]. The PROM will be assessed by the patient filling in the validated questionnaires (EQ-5D-5L, ATRS, FAOS, OMAS) at the 1 year visit at the physiotherapist, who will also perform the functional evaluations, i.e. heel-rise tests. If any patient will miss the 1 year visit, the questionnaires will be sent home to the patient.

An IPC effect on tissue healing will be corroborated by assessment of callus production. Callus production in ATR and AF patients is assessed at 6 weeks by microdialysis followed by quantification of procollagens[15].

To further control that the outcome measures are registered correctly, independent data monitoring and help with data management will be performed by eg. Karolinska Trial Alliance (KTA). Major outcome events (including serious adverse events believed to be due to treatment) will be supplied. All data will be reported using an online system registration at Karolinska Institutet called RedCap, which is a validated patient reporting tool used at over 300 universities.

Trial Organization: The Steering Committee will consist of Paul Ackermann (PI), Bengt Eriksson (VTE expert), Lasse Lapidus (VTE expert), Fausto Labruto (Radiologist, compression Doppler ultrasound), Gunnar Edman (Statistician), Luigi Belcastro (coordinating study nurse), Kenneth Jonsson (bone healing), Jon Karlsson (expert on patient-reported outcome), and Therese Djärv (Patient representative).

National collaborators from 12 regions in Sweden, 23 hospitals, have already agreed to participate in this multicenter study. Stockholm region: Karolinska University Hospital Solna and Huddinge, Danderyd Hospital, Stockholm South General Hospital, Södertälje and Norrtälje Hospital. Uppsala region: Uppsala University Hospital. Östergötland region: Linköping University Hospital. Gotland region: Visby lasarett. Skåne region: Skåne University Hospital in Lund and in Malmö. Halland region: Kungsbacka Hospital. Västra Götalands region: Sahlgrenska University Hospital, Östra Hospital, Kungälv Hospital. Värmland region:

Karlstad Central Hospital. Gävleborg Region: Gävle and Bollnäs Hospital. Västerbotten region: University Hospital Umeå. Örebro: University Hospital Örebro, Karlskoga lasarett, Lindesberg lasarett. Jönköping region: Eksjö Hospital.

International collaborators from Rizzoli hospital in Bologna, Italy have shown interest to participate.

Estimated sample size and power

We plan to include at least 1400 patients, with 10% drop-out accounted for, although our earlier study demonstrated a 5.3% drop-out[9]. Many patients will in clinical routine receive LMWH, which is accounted for. This gives the trial 90% power (alpha 0.05) to identify an absolute risk reduction of 8% (28% vs. 20%) and relative risk reduction of 29% in primary outcome. The expected relative risk reduction is higher, 40%, and the minimum clinical relevant absolute risk reduction in primary outcome between the groups is 4% based on recent studies[9 26].

The frequency of our primary outcome is given from recent studies showing a 50% rate of CDU-verified DVTs after ATR and 25% rate after ankle fracture (AF)[9 27]. This gives a total DVT-rate of 33% when including two AF for every ATR. As extra precautions we reduced the expected total DVT-rate from 33% to 28% and reduced the relative risk reduction from 40% to 30%.

The 1400 included patients will consist of at least 400 ATR- and at least 1000 AF-patients, with the same drop out as above. For subgroup analyses (ATR / AF) this gives the trial 80% power (alpha 0.05) to detect a 30% relative risk reduction and an absolute risk reduction of 8% (25% vs. 17%) for AF and 15% (50% vs. 35%) for ATR in primary outcome.

The mean inclusion per hospital is (one)-two AF each week and one ATR every second week, which totals at least a mean of 75 patients/hospital/year[9]. With 1,5 patients included per week per each hospital (20 hospitals registered), we will finish inclusion within one year.

For the secondary patient-reported outcomes, the trial has more than 95% power (alpha 0.05) to identify a clinically relevant difference, which at one year is 10 points difference on the rating scales (0-100)[20]. For the explanatory VTE-preventive mechanisms (blood serum test) and collagen production (microdialysis) earlier studies demonstrate that a sample size of 100 gives 90% power to detect significant differences between groups, which will save expenses.

Treatment compliance of the patients, which was 91% in our earlier study, will be registered both by the IPC-device and by the patient. Patients will daily register the number of hours that IPC was used.

Material: Patient selection – population, sample

Male and female patients aged between 18 and 75 years with an acute injury requiring lower-leg immobilization, i.e. acute unilateral ATR or isolated AF, in a hospital setting will be eligible. The exclusion criteria will be: inability to give informed consent; planned follow-up at another hospital; renal failure; heart failure with pitting oedema; thrombophlebitis; malignancy; peripheral vascular disease; haemophilia/thrombophilia and pregnancy [9].

The randomising clinician or nurse will screen for eligible patients as soon after their presentation to hospital as possible. To minimize differences between hospitals, patients will be eligible for inclusion if treatment starts within 10 days after the injury. IPC-prophylaxis for

DVT may have greater effect if started early after injury, but these potential differences will also be considered below. The responsible clinician collects the baseline data necessary to complete a randomization form. He/she then will randomize patients via a central, web-based service (RedCap) by giving the baseline data (which are then stored securely) and receives the treatment allocation at the end of the session.

The randomisation form should be filed in the patient's medical notes, along with one copy of the signed informed consent form and patient brochure. The patient should receive a patient brochure along with a signed copy of the consent form. Copies should also be kept in the site file. The treatment allocation will be blinded for the assessors of outcome; i.e. ultrasonographists doing the CDU, physiotherapists or nurses performing the patient reported outcomes. The IPC-therapy will, due to its nature, not be blinded to the patient and the clinician applying the therapy.

Statistical analysis plan (Gunnar Edman, statistician)

All analyses will be based on intention to treat. We will analyze patients in the groups they are randomized to, regardless of treatment received. A patient might be withdrawn because of severe non-adherence or withdrawal of consent by the patient. For binary outcomes (e.g. occurrence of a primary or secondary outcome OR not), outcomes will be presented as odds ratios and 95% confidence intervals, adjusted using logistic regression for the factors used in the minimization algorithm and weight-bearing. We will calculate absolute reductions in risk from these values, as presented in the reference with similar study design[26].

Group differences for ordinal secondary outcome data, such as the patient-reported data (ATRS and OMAS), will be analyzed by nonparametric tests[20]. Group differences for EQ5D-5L (index scale), FAOS (ratio scale) and continuous secondary outcome data will be analyzed by t-tests if the data are normally distributed, and using an appropriate nonparametric test otherwise.

Subgroup analyses will be performed to determine whether certain types of patients might gain greater or less benefit from IPC. We will estimate the effect of treatment allocation on the primary outcome subdivided by key baseline variables and adjusted for the other factors included in the minimization algorithm. Subgroup analyses will be performed by observing the change in log-likelihood when the interaction between the treatment and the subgroup is added into a logistic regression model. We will determine whether there is significant heterogeneity between these subgroups. The following preplanned subgroup analyses will be performed:

Is IPC more effective in patients at higher risk of DVT? It seems likely that patients at higher risk of DVT might gain greater benefit from IPC than those at lower risk. Patients with ATR exhibit higher risk of DVT than patients with AF, and patients aged ≥ 40 years exhibit almost fivefold higher odds of developing DVT[9]. Moreover, prior history of DVT, weight-bearing, and surgery are likely to affect the risk of DVT. Therefore, we will undertake subgroup analyses of the effect of allocation to IPC on the primary outcome among patients with and without at least one of these factors at baseline.

Analysis of impact of delay in applying IPC? There is often a delay in presenting or being treated with a lower limb injury (ATR/AF) and therefore this can lead to a delay in applying VTE prophylaxis. Moreover, patients may even suffer a VTE before treatment is initiated. Thus, we hypothesize that IPC will reduce the frequency of the primary outcome to a greater

extent among patients enrolled early compared to later. We will therefore examine the effect of treatment among patients enrolled early versus later after injury.

Compliance and duration of treatment with IPC? IPC compliance was 91% in our recent trial, but has usually been used for a relatively short time on perioperative patients and in outpatients. There is a concern that IPC may not be used for the whole six weeks or that it will not be applied continuously. We will therefore carry out additional analyses in order to determine how IPC- compliance affects the primary outcome.

Economic analyses: Economic analysis of the trial treatment effects will involve a within-trial evaluation of cost effectiveness integrated into a decision-analytic model of longer run costs and health effects. The within-trial analysis will be conducted on an intention-to-treat basis. The primary health endpoints will be VTE times adjusted for patient reported outcome.

A societal perspective will be taken for assessing costs of patient´s care during the six-week immobilization. Patient-specific hospital resource use will be measured. The net direct medical cost will include a cost estimate of IPC capital/equipment (and staffing implications) and the averted costs arising from the effects of IPC on expected DVT/PE incidence. Probabilistic sensitivity analysis will also be used to assess the hospital cost distributions.

Specific intermediate objectives

The Steering Committee will meet every 4th month. Milestones at these meetings will consist of an inclusion rate of at least 200 patients/4 months, adequate data monitoring by Karolinska Trial Alliance and that the primary outcome has been reported in more than 80% of the patients. If the inclusion rate drops significantly below 200 patients, then more hospitals will be included in the study. These milestones will be reported to the Swedish Research Council.

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