BMJ Open

A cohort feasibility study of an intermittent pneumatic compression device within a below-knee cast for the prevention of venous thromboembolism

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012764
Article Type:	Research
Date Submitted by the Author:	22-May-2016
Complete List of Authors:	Braithwaite, Irene; Medical Research Institute of New Zealand, De Ruyter, Bernadette; Capital and Coast District Health Board, Orthopaedic Department Semprini, Alex; Medical Research Institute of New Zealand, Ebmeier, Stefan; Medical Research Institute of New Zealand Kiddle, Grant; Capital and Coast District Health Board, Orthopaedic Department Willis, Nigel; Capital and Coast District Health Board, Orthopaedic Department Carter, John; Capital and Coast District Health Board, Haematology Department Weatherall, Mark; University of Otago Wellington, Beasley, Richard; Medical Research Institute of New Zealand; Capital and Coast District Health Board, Respiratory Department
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Haematology (incl blood transfusion), Sports and exercise medicine
Keywords:	Bleeding disorders & coagulopathies < HAEMATOLOGY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Foot & ankle < ORTHOPAEDIC & TRAUMA SURGERY, VASCULAR MEDICINE

A cohort feasibility study of an intermittent pneumatic compression device within a below-knee cast for the prevention of venous thromboembolism

Irene Braithwaite, *Medical Research Fellow*[1,2], Bernadette De Ruyter, *Orthopaedic Nurse*[2], Alex Semprini, *Medical Research Fellow*[1], Stefan Ebmeier, *Medical Research Fellow*[1], Grant Kiddle, *Orthopaedic Consultant*[2], Nigel Willis, *Orthopaedic Consultant*[2], John Carter, *Consultant Haematologist*[2], Mark Weatherall, *Statistician*[3], Richard Beasley, *Director, Respiratory Physician*[1,2]

[1]Medical Research Institute of New Zealand, Wellington, New Zealand,
[2]Capital and Coast District Health Board, Wellington, New Zealand
[3]University of Otago Wellington, Wellington, New Zealand

Key Words: Cast Immobilisation, Lower extremity, Venous thromboembolism, Pulmonary embolism, Deep vein thrombosis, intermittent compression

Word Count: Abstract (261) manuscript: (2,932), tables: 2, figures: 3

Short title: Foot pump compression, lower limb immobilisation and VTE prevention

Correspondence:

Dr Irene Braithwaite
Medical Research Institute of New Zealand
Private Bag 7902, Wellington 6242
New Zealand
Telephone: 64-4-805 0245
Fax: 64-4-389 5707
Email: Irene.braithwaite@mrinz.ac.nz

ABSTRACT

Objectives: To determine the likely enrolment rate of eligible participants into a randomised controlled trial (RCT) in which a within-cast intermittent pneumatic compression device using Jet Impulse Technology (IPC/JIT) is one of three possible interventions in a RCT for prevention of venous thromboembolism (VTE) in the clinical setting of isolated lower limb cast immobilisation.

Design: A prospective, open-label feasibility study of the IPC/JIT device placed within a lower limb cast.

Setting: Wellington Regional Hospital Fracture Clinic

Participants: Individuals aged 18 to 70 who presented with a lower limb injury requiring a minimum of four weeks below-knee cast immobilisation.

Intervention: Placement of an IPC/JIT device within lower limb cast.

Outcome measures: The main outcome measure was the proportion of eligible participants who participated in the feasibility study. Secondary outcome measures included adherence to device utilisation throughout the study, ease of application of the device and adverse events potentially associated with its use.

Results: The proportion of potentially eligible participants for the IPC/JIT device was only 7/142 (5%), 95% CI 2 to 9.9. Devices were used for a mean (range) of 4.1 (1.9 to 10.2) hours per day and none of seven participants had adequate adherence to the device. Three of the seven participants suffered an adverse event, including one DVT, one dorsal foot ulcer and one skin maceration.

Conclusions: A within-cast IPC/JIT device is unlikely to be a feasible randomisation arm for a RCT assessing possible interventions for the reduction of VTE risk in the clinical setting of lower limb injury requiring below knee cast immobilisation for a minimum of four weeks.

Trial registration: This trial was prospectively registered (ANZCTR 12615000192583 and was approved by the New Zealand Health and Disability Ethics Committees (14/STH/138/AM03).

STRENGTHS AND LIMITATIONS OF THIS STUDY:

This study is generalizable to all adults presenting with acute injury requiring lower limb cast immobilisation.

Data reflecting intermittent pneumatic compression device usage was downloaded directly from the machines and was not dependent on participant self-reporting.

Assessment of adverse events and VTE rates was limited by low recruitment into the study.

INTRODUCTION

Prolonged cast immobilisation of the lower limb after injury is associated with an increased risk of venous thromboembolism (VTE).[1–7] In a recent analysis of risk factors for VTE in two case-control studies, we found lower limb immobilisation was associated with a 73- fold increased risk of VTE.[8] Lower limb immobilisation was the most common potentially preventable cause of VTE in the 18 to 65 year age group, being present in one in seven cases.

A 2014 Cochrane review of low molecular weight heparin (LMWH) for prevention of VTE in patients with lower limb immobilisation reported a wide range, between 4.3% and 40%, for the incidence of VTE detected by radiological screening in patients in the control arms of these studies.[1] The risk of VTE was reduced by the administration of LMWH by approximately 50%. The risk reduction was similar in those with tendon ruptures compared to fractures, and for surgically compared to conservatively treated patients. Widespread use of LMWH could expose a potentially large patient group to the bleeding risks of its use and the American College of Chest Physicians (ACCP), in their Evidence-based Clinical Practice Guidelines on Prevention of Thrombosis (2012),[9] ,suggests that the risks and benefits of VTE prophylaxis are fairly evenly balanced and recommend no prophylaxis for cast immobilisation in isolated lower leg injuries distal to the knee. They also suggest that further research in this area is required.

In New Zealand LMWH for the prevention of VTE in the clinical setting of lower limb immobilisation is not funded for outpatients and its use has practical difficulties with patient adherence to a daily sub-cutaneous injection regime. Some evidence supports the use of low dose oral aspirin prophylaxis for VTE in a variety of medical and surgical patient groups.[10,11] A single large randomised placebo-controlled trial of low dose aspirin in hip fracture and elective arthroplasty found a one third reduction in VTE risk with only a small increase in post-operative bleeding.[12] There are no trials of low dose aspirin in lower limb immobilization. In an audit in our local

institution carried out after the introduction of aspirin 100mg daily for prophylaxis of VTE, we could identify no change in VTE rates. This suggests that aspirin is not an effective prophylactic measure in this clinical setting.[13] Oral anticoagulants including direct factor Xa inhibitors, such as rivaroxaban and apixaban, reduce the risk of VTE in total hip and knee arthroplasty with a favourable efficacy/risk profile compared with LMWH,[11,14] however their efficacy and safety profile in lower limb immobilisation is yet to be assessed. The clinical effectiveness of intermittent pneumatic compression (IPC) systems in the prevention of DVT is well established as a non-pharmacological alternative for VTE prevention without the risk of bleeding.[9,15]

When this current study was planned, there were no trials of IPC devices in the setting of prolonged lower limb cast immobilisation. The potential for its use in this clinical situation was supported by our demonstration that IPC devices increase popliteal vein blood flow within a lower limb cast.[16] This current study was a feasibility study of the use of IPC technology within lower limb casts. It aimed to estimate recruitment rates for a possible large-scale randomised controlled trial, the tolerability of IPC/JIT placement under a lower limb cast for a protracted period of time (a minimum of four weeks duration, with cast changes of up to two weeks apart), adherence to the proposed IPC/JIT in-cast regime, and adverse events potentially associated with its use. We were also interested in the proportion of potential participants who might not be eligible for recruitment to a trial arm that included the use of Rivaroxaban based on already using an oral anticoagulant, being at very high risk of VTE, being treated for active upper gastro-intestinal ulcer disease, immobility > 2 days prior to enrolment, significant liver disease, creatinine clearance <30ml/min), or concomitant use of HIV protease inhibitors.

PARTICIPANTS AND METHODS

Recruitment for the feasibility study occurred for six months, August 2015 to January 2016, with a further three months for follow-up of participants. Eligible participants were patients aged between 18 and 70 years presenting to Wellington Hospital Fracture Clinic with ruptured Achilles tendon, stable ankle fracture requiring a non-weight bearing cast, or, if possible, ankle fracture with operative fixation and then cast immobilisation. Exclusion criteria included patients with a high risk for VTE, active gastric or duodenal ulcer, already using anticoagulation, immobility >2 days before enrolment, significant liver disease (including moderate to severe hepatic impairment especially when associated with coagulopathy), renal impairment (estimated creatinine clearance <30ml/min), or concomitant use of HIV protease inhibitors.

Initially recruitment was limited to working hours however we identified that many potentially eligible participants presented on weekends, and so recruitment was extended to include weekends. Investigators and orthopaedic nursing staff identified potentially eligible participants, informed them about the open-label trial, and asked them if they would like to participate. Those who declined to participate were asked if the reason for not participating was because the treatment is a device rather than a medication. A record was kept of potential participants, including those who were treated and discharged outside of working hours, and of all potential participants approached during the working day. This record was used to identify the proportion of eligible participants likely to be recruited into the proposed RCT.

Participants who agreed to be enrolled into the feasibility trial had the IPC with Jet Impulse Technology (JIT) placed under their lower limb cast (Figure 1) and the usual care of aspirin EC 100mg daily was also prescribed. They were reviewed fortnightly at the fracture clinic for up to eight weeks. In-cast pad changes were planned at weeks two and four and possibly six depending on adherence of participants to the device and the treatment plans of the orthopaedic consultant. Participants were asked to use the IPC/JIT while they were seated or immobile during the day and

while in bed at night. As assessment of the total time, in hours, of IPC/JIT device usage was collected. Good adherence was defined as 60% of the potential time available, namely whether this exceeded 14.4 hours per day. Participants who withdrew from the study were asked if the reason for this was related to discomfort or adverse events from using the device. At clinic visits, nursing staff completed a semi-structured record regarding the practicalities of device placement and related issues such as skin condition.

The VADOplex® VenaJet foot pump system (OPED, Oberlaindern, Germany) works with Jet Impulse Technology (JIT), to mimic the usual weight-bearing walking process. It comprises a 4.6kg, 320mm wide x 190mm high x 200mm deep (including mounting handle), bilateral pump unit, with an in-cast pad that is attached to the pump unit via an air tube (Figure 2). The pump mechanism mimics the natural full weight-bearing walking process, rapidly inflating a distal air-cell in the foot cuff to 130mmHg, which then settles to 52mmHg, followed by a proximal air-cell 0.3 seconds later, settling to 48mmHg. After 6 seconds of compression at 48 to 52mmHg, both air-cells deflate. This cycle is repeated every minute. The total hours the device has been in use, both with the garment in operation, and without the garment, is indicated on the device readout. These numbers were documented at each visit.

All participants were scheduled for ultrasound examination of the popliteal to femoral vein of the affected limb (accessible above the leg cast) prior to each clinic visit, and again for ultrasound of the entire limb after removal of the cast or moonboot at the end of their orthopaedic treatment period which was expected to be between six and eight weeks. At any time between clinic visits and during the ensuing six week follow up period, if participants experienced signs or symptoms of DVT or PE, they would have an ultrasound or computed tomography pulmonary angiogram (CTPA) respectively, and be treated according to Wellington Hospital protocols. All participants were educated about the symptoms of DVT and PE and advised to seek medical review should these occur. A final follow up

phone call was done six weeks after completion of cast-immobilisation treatment to ensure there had been no VTE event after completing the study.

Sample size and statistical methods

A total of 70 participants in the feasibility trial provided over 95% power to rule out a recruitment rate of less than 50%. It also provided 80% power with an alpha of 5% to rule out a complication rate of at most 33% if the anticipated complication rate was 10%; and to rule out adherence of less than 60% if the adherence rate was 75%. The main analyses planned were to estimate 95% confidence intervals proportions by the exact Clopper-Pearson method and to compare the achieved proportions with those outlined in the sample size calculation.

SAS version 9.4 was used.

RESULTS

The flow of potentially eligible participants is shown in Figure 3. Only 7/142 (5%) of potentially eligible participants were enrolled (Table 1), with an exact 95% CI of 2% to 9.9%, P-value for comparison with a rate of 50% <0.001. There were 58 (41%) potentially eligible participants who were not enrolled for logistics reasons; 39(27%) were admitted for operative intervention, and due to theatre logistics, could not be enrolled and 19 (13%) presented on weekends and evenings before the change in study protocol. There were 77 (54%) potentially eligible participants who were not enrolled due to reasons that were not anticipated at the time of design of the feasibility study, such as a moulded cast preventing the placement of the IPC/JIT, living out of geographical area thus making follow-up of participants impracticable, frailty of potential participants and use of a Plaster of Paris cast, the integrity of which might be impaired by the IPC/JIT device. Six potential participants declined due to the perceived impracticality of using the IPC/JIT device. There were no documented issues with skin integrity at initial device and cast placement. There were no issues with initial device placement by fracture clinic staff. A description of all 142 potential participants is shown in Table 2.

Table 1. Flow of potential participants through the feasibility study

Recruitment status, N=142	N (%)
Not enrolled – Logistic Reasons	**58 (40.8)**
- Operative intervention	39 (27.5)
- Weekend and evenings	19 (13.4)
Not enrolled – Other reasons	**77 (54.2)**
- Moulded cast	31 (21.8)
- Out of geographical follow up area	10 (7.0)
- Frailty	10 (7.0)
- Plaster of Paris cast – not suitable	9 (6.3)
Not enrolled – Due to exclusion criteria	**11 (8.2)**
- Injury >48 hours prior	8 (5.8)
- Weight bearing cast applied	2 (1.4)
- Other VTE risk factor	1 (1)
Declined study	**6 (4.2)**
Enrolled in study	**7 (5.0)**
Total	**142**

Table 2. Description of potential and enrolled participants in feasibility study

	Not recruited (N=135)	Recruited (N=7)
Continuous variables	**Mean (SD)**	
Age (years)	43.1 (15.0)	39.4 (7.9)
Categorical variable	**N (%)**	
Female	75 (56)	3 (43)
Ethnicity		
- European	87 (64.4)	2 (28.6)
- Maori	19 (14.1)	3 42.9)
- Pacific Island	11 (8.1)	2 (28.6)
- Asian	10 (7.4)	0 (0)
- Other	8 (5.9)	0 (0)
Day presenting		
- Monday	23 (17.0)	2 (28.6)
- Tuesday	19 (14.1)	1 (14.3)
- Wednesday	19 (14.1)	1 (14.3)
- Thursday	10 (7.4)	1 (14.3)
- Friday	22 (16.3)	1 (14.3)
- Saturday	27 (20.0)	0 (0)
- Sunday	15 (11.1)	1 (14.3)
Injury		
- Ankle Fracture	64 (47.4)	1 (15)
- Achilles tendon	42 (31.1)	6 (85)
- Fibula Fracture	13 (10.4)	-
- Other injury	16 (11.1)	-

Participants enrolled to use the IPC/JIT device

Of the seven participants enrolled in the feasibility study three participants did not complete the minimum four week period of IPC/JIT usage; one changed to a weight bearing cast after one week and the device was removed, one withdrew after developing an ulcer on the dorsum of their foot in the initial two week period, and one withdrew after two weeks due to maceration of the skin. Four participants completed four weeks of IPC/JIT device usage. One participant that completed the four week intervention had a DVT diagnosed at scheduled four week ultrasound, and was treated with rivaroxaban. No participants developed symptomatic VTE in the six week follow up period. Excluding the participant who changed to a weight-bearing cast the complication rate was 3/6 (50%) with 95% CI of 11.8 to 88.2; P-value for a comparison with 33% of 0.63.

Participant adherence to JIT and feedback about the device

The seven participants were issued the IPC/JIT devices and used the device for a total of 148 days. For these participants a total of 608 hours of use were recorded. The mean (range) of daily use was 4.1 hours (1.9 to 10.2). No participant met the proposed adherence target of an average of 14.4 hours per day in any of the two-week periods with a 95% confidence interval for adherence of 0 to 41%, P-value for comparison with 60%, 0.003. Of the seven participants, six did not use the device at night as it interfered with their sleep. All participants found the pump unit difficult to move around while they were non weight-bearing and on crutches, and tended to leave the pump unit in a single location where they were likely to spend most of their time. One participant attempted to take the pump unit to and from work, but found even with a backpack, that the pump unit was too large and awkward to carry around while on crutches. All participants indicated that they would use an IPC/JIT system again, but that the pump unit would have to be much smaller and lighter to allow ease of use.

Exclusion criteria for rivaroxaban arm of proposed RCT

Of the 142 potentially eligible participants identified in the study, 5 (3.5%) were already prescribed an anticoagulant, 3 (2.1%) had a high risk of VTE (two had active nephritis and one had a history of VTE) and 1 (0.7%) was on treatment for an active gastric ulcer. In all 9/142 (6.3%) would not have been eligible for Rivaroxaban treatment, 95% CI 2.9 to 11.7. None of the remaining 133 (91.7%) participants had any of the remaining exclusion criteria: immobility > 2 days prior to enrolment, significant liver disease, creatinine clearance <30ml/min) or concomitant use of HIV protease inhibitors.

DISCUSSION

This feasibility study shows that the IPC device utilising JIT technology is not a feasible randomisation arm in a RCT assessing VTE prevention rates in lower limb immobilisation. Furthermore, it is clearly not a therapeutic option for VTE prophylaxis in this clinical setting, regardless of its potential efficacy.

It was interesting to compare outpatient utilisation of the IPC/JIT device when compared to studies of foot IPC use within hospital inpatient settings. In a study of patients after a total joint arthroplasty Pitto and Young reported that while 5% of patients discontinued IPC use between two and six days after initiation of use, foot pump devices had been used by the remaining 95% of patients for 15.9 hours daily.[17] Charalambous and colleagues assessed adherence to foot-pump usage in an inpatient setting after joint arthroplasty, and found that as patients got in and out of bed more frequently, their foot pumps were re-applied less often, and that only 60% of patients used foot pumps at night when confined to bed.[18] In our study, the IPC/JIT device was used for four hours/day and six of seven participants did not use the device at night. It is likely that in an unsupervised environment participants may be less likely to utilise the device, particularly overnight compared to an inpatient group. Adherence might be improved by utilising a smaller, more portable pump unit that was easier for participants to move around with. Providing more than one of the current devices to each participant to allow placement at strategic locations at home or at work, while possible, is likely to prove too expensive.

It is informative to compare the complications associated with IPC/JIT use in this study with those experienced in other trials. Two out of seven (28.5%) participants suffered complications associated with the JIT device; one a dorsal foot ulcer and one who suffered skin maceration. This is higher than skin-related adverse events reposted in previous studies where dorsal ulcers, skin blisters and

malleolar sores have been reported in 0% of 42 patients after hip surgery,[19] 6.7% of patients receiving plantar venous compression after total hip arthroplasty,[20] 4.5% in patients using a plantar compression device after total hip replacement[21] and 7.5% of patients using pre-operative plantar compression after ankle fracture.[22] Skin maceration is not uncommon within fibreglass casts, due either to excess sweating or inadvertent wetting of the cast, thus we were uncertain that the IPC/JIT device was the direct cause of the maceration. After this event, we started placing more protective material between the footpad and the skin and no further episodes occurred.

Foot pump devices have been shown to increase lower limb venous flow,[23–25] and a number of early studies have shown that foot pump prophylaxis with or without graduated compression stockings and/or pharmacological prophylaxis significantly reduces the risk of VTE after major orthopaedic surgery compared to; compression stockings alone,[26] or compression stockings and heparin.[20,21] These findings, in conjunction with the high rates of VTE found in the clinical setting of lower limb immobilisation,[1,13,27] raise the question of potential IPC/JIT prophylaxis in this situation, which would eliminate the risk of bleeding that exists with pharmacological prophylaxis. Since the inception of this feasibility study, Domeij-Arverud and colleagues[28] have published findings related to the use of an IPC and plastic foot cuff under a Plaster of Paris cast after Achilles tendon repair. They found that nine of 14 participants randomised to IPC treatment and six of 12 who received no intervention developed DVT during the intervention period. IPC malfunction and the need to replace the cast correlated with a higher risk of VTE at 2 weeks resulting in the study being halted, suggesting that IPC prophylaxis in this clinical setting is no better than, and in fact is possibly worse than no prophylaxis. In our study, we enrolled only patients with fibreglass casts, there were no IPC/JIT malfunctions and no unscheduled cast changes were necessary. One in seven participants in our study was found to have a DVT on radiological screening, however given the small number of participants that utilised the IPC/JIT in this study, we cannot draw a conclusion about the likely VTE rates with this intervention.

If the randomised treatment was dropped from the proposed RCT, and all the limiting logistics factors of the non-recruited group were suitably addressed e.g. full out of hours recruitment; access to the operating theatre post-operatively for device placement, about 130 patients would be eligible in each six month period. In this modified RCT, 200 participants would be required in each treatment arm (a total of 400) to ensure 90% power with an alpha of 5% to detect a 50% relative reduction in VTE events with rivaroxaban compared to the control arm (aspirin), assuming a 20% drop out rate. This suggests that the single Wellington Hospital site would have the potential to fully recruit the proposed RCT within a two year period, even if the recruitment rate was 80%.

Conclusions

The IPC/JIT device placed within a lower limb fibreglass cast is not a feasible randomisation arm for the proposed RCT investigating the rates of VTE in the clinical setting of outpatient temporary lower limb immobilisation due to low recruitment rates, poor adherence to treatment regimens and high rates of adverse events. The characteristics of potential participants suggest that recruitment into the rivaroxaban and aspirin arms of the proposed RCT from a single location is achievable.

STATEMENTS

Contributorship.

Study concept and design: R Beasley, I Braithwaite, M Weatherall, B De Ruyter, Grant Kiddle, Nigel Willis, John Carter. Acquisition of Data: I Braithwaite, B De Ruyter, A Semprini, S Ebmeier. Drafting of the manuscript: R Beasley, I Braithwaite. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: I Braithwaite, M Weatherall. Administrative, technical and material support: All authors. Study supervision: I Braithwaite.

Funding: The JIT devices were supplied by Dickson and Dickson Healthcare Ltd for the purposes of undertaking the study. The study was funded by the Health Research Council of New Zealand (HRC) through a feasibility grant (14/570), the first author was funded through the Health Research Council of New Zealand (HRC) by way of a Clinical Training Fellowship to undertake a PhD (14/040), and the Medical Research Institute of New Zealand also receives funding from the HRC through the Independent Research Organisations Capability Fund (14/1002). The funding parties had no involvement in the design or preparation of the study, collection, analysis and interpretation of the data, or the decision to submit for publication.

Competing Interests Statement: The authors have no competing interests to declare.

Guarantor: Dr I Braithwaite had access to all the data on the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the data being reported; that no important aspects of the analysis have been omitted; and that any discrepancies from the analysis as planned (and, if relevant, registered) have been explained

Data sharing statement: Patient level data available from the corresponding author on request. Consent was not obtained from participants for data sharing, but the presented data are anonymised and the risk of identification is low.

REFERENCES

1 Testroote M, Stigter-Willem a H, Janssen L, *et al.* Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. *Cochrane Database Syst Rev* 2014;4:CD006681.

2 Ettema HB, Kollen BJ, Verheyen CCPM, *et al.* Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. *J Thromb Haemost* 2008;6:1093–8.

3 Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N Engl J Med* 2002;347:726–30.

4 Lapidus LJ, Ponzer S, Elvin A, *et al.* Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. *Acta Orthop* 2007;78:528–35.

5 Lapidus LJ, Rosfors S, Ponzer S, *et al.* Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. *J Orthop Trauma* 2007;21:52–7.

6 Jorgensen PS, Warming T, Hansen K, *et al.* Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. *Thromb Res* 2002;105:477–80.

7 Kock HJ, Schmit-Neuerburg KP, Hanke J, *et al.* Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. *Lancet* 1995;346:459–61.

8 Braithwaite I, Healy B, Cameron L, *et al.* Lower limb immobilization and venous thromboembolism risk : combined case-control studies. *Submitted to JBJS* 2016.

9 Falck-Ytter Y, Francis CW, Johanson NA, *et al.* Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*;141:e278S – 325S.

10 Collins R, Baigent C, Sandercock P, *et al.* Antiplatelet therapy for thromboprophylaxis: the need for careful consideration of the evidence from randomised trials. Antiplatelet Trialists' Collaboration. *BMJ* 1994;309:1215–7.

11 Eriksson BI, Kakkar AK, Turpie AG, *et al.* Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *J Bone Jt Surg Br* 2009;91:636–44.

12 Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;355:1295–302.

13 Braithwaite I, Dunbar L, Eathorne A, *et al.* Venous thromboembolism rates in lower limb immobilization after Achilles tendon injury unchanged after introduction of prophylactic aspirin: audit. *J Thromb Haemost* 2016;14:331–5.

14 Lassen MR, Ageno W, Borris LC, *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776–86.

15 Niikura T, Lee SY, Oe K, *et al.* Incidence of venous thromboembolism in fractures around and below the knee with physical prophylaxis. *Orthopedics*;35:e1476–82.

16 Braithwaite I, Mackintosh S, Buchanan S, *et al.* Venous haemodynamics of Jet Impulse Technology within a lower limb fibreglass cast : a randomised controlled trial (JIT in-cast trial). *Submitted to JRSM Open* 2015.

17 Pitto RP, Young S. Foot pumps without graduated compression stockings for prevention of deep-vein thrombosis in total joint replacement: Efficacy, safety and patient compliance - A comparative, prospective clinical trial. *Int Orthop* 2008;32:331–6.

18 Charalambous C, Cleanthous S, Tryfonidis M, *et al.* Foot pump prophylaxis for deep venous thrombosis - Rate of effective usage following knee and hip arthroplasty. *Int Orthop* 2003;27:208–10.

19 Asano H, Matsubara M, Suzuki K, *et al.* Prevention of pulmonary embolism by a foot sole pump. *J Bone Joint Surg Br* 2001;83:1130–2.

20 Bradley JG, Krugener GH, Jager HJ. The effectiveness of intermittent plantar venous compression in prevention of deep venous thrombosis after total hip arthroplasty. *J Arthroplasty* 1993;8:57–61.

21 Santori FS, Vitullo A, Stopponi M, *et al.* Prophylaxis against deep-vein thrombosis in total hip replacement. Comparison of heparin and foot impulse pump. *J Bone Jt Surg - Ser B* 1994;76:579–83.

22 Caschman J, Blagg S, Bishay M. The efficacy of the A-V Impulse system in the treatment of posttraumatic swelling following ankle fracture: a prospective randomized controlled study. *J Orthop Trauma* 2004;18:596–601.

23 Charles T, Mackintosh S, Fingleton J, *et al.* Efficacy of micromobile foot compression device in increasing lower limb venous blood flow. *Int J Vasc Med* 2013;2013:948769.

24 Delis KT, Slimani G, Hafez HM, *et al.* Enhancing venous outflow in the lower limb with intermittent pneumatic compression. A comparative haemodynamic analysis on the effect of foot vs. calf vs. foot and calf compression. *Eur J Vasc Endovasc Surg* 2000;19:250–60.

25 Morris RJ, Woodcock JP, Pitto RP, *et al.* Evidence-Based Compression. *Int Orthop* 2004;239:162–71.

26 Fordyce MJ, Ling RS. A venous foot pump reduces thrombosis after total hip replacement. *J. Bone Joint Surg. Br.* 1992;74:45–9.

27 Healy B, Beasley R, Weatherall M. Venous thromboembolism following prolonged cast immobilisation for injury to the tendo Achillis. *J Bone Jt Surg Br* 2010;92:646–50.

28 Domeij-Arverud E, Latifi A, Labruto F, *et al.* Can foot compression under a plaster cast prevent deep-vein thrombosis during lower limb immobilisation? *Bone Joint J* 2013;95-B:1227–31.

FIGURE LEGENDS

Figure 1. JIT/IPC footpad placement under lower limb cast

Figure 2. JIT/IPC device

Figure 3. Flow of participants through study

Figure 1. JIT/IPC footpad placement under lower limb cast

250x321mm (300 x 300 DPI)

Figure 2. JIT/IPC device

250x170mm (300 x 300 DPI)

Figure 1: Flow of eligible participants in study

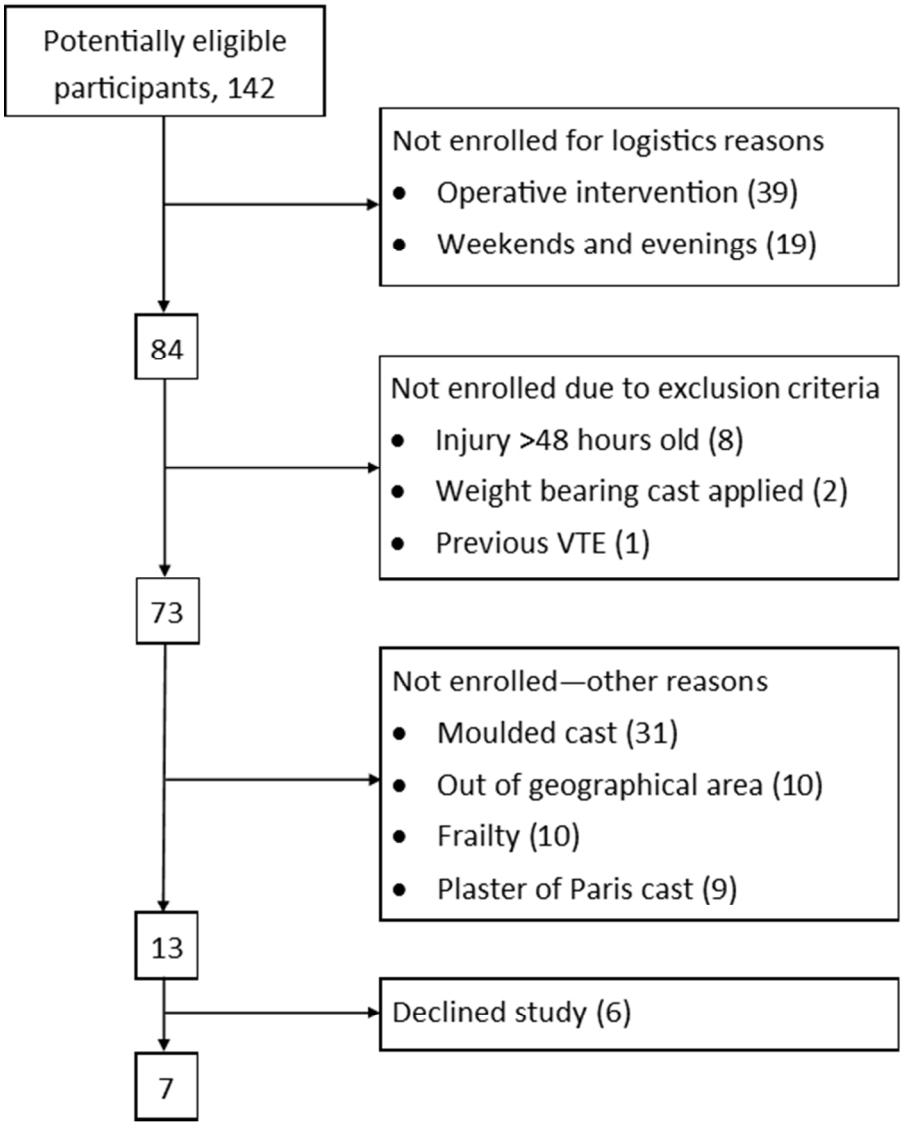


Figure 3. Flow of participants through study

48x65mm (300 x 300 DPI)

BMJ Open

A cohort feasibility study of an intermittent pneumatic compression device within a below-knee cast for the prevention of venous thromboembolism

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012764.R1
Article Type:	Research
Date Submitted by the Author:	24-Jul-2016
Complete List of Authors:	Braithwaite, Irene; Medical Research Institute of New Zealand, De Ruyter, Bernadette; Capital and Coast District Health Board, Orthopaedic Department Semprini, Alex; Medical Research Institute of New Zealand, Ebmeier, Stefan; Medical Research Institute of New Zealand Kiddle, Grant; Capital and Coast District Health Board, Orthopaedic Department Willis, Nigel; Capital and Coast District Health Board, Orthopaedic Department Carter, John; Capital and Coast District Health Board, Haematology Department Weatherall, Mark; University of Otago Wellington, Beasley, Richard; Medical Research Institute of New Zealand; Capital and Coast District Health Board, Respiratory Department
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Haematology (incl blood transfusion), Sports and exercise medicine
Keywords:	Bleeding disorders & coagulopathies < HAEMATOLOGY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Foot & ankle < ORTHOPAEDIC & TRAUMA SURGERY, VASCULAR MEDICINE

A cohort feasibility study of an intermittent pneumatic compression device within a below-knee cast for the prevention of venous thromboembolism

Irene Braithwaite, *Medical Research Fellow*[1,2], Bernadette De Ruyter, *Orthopaedic Nurse*[2], Alex Semprini, *Medical Research Fellow*[1], Stefan Ebmeier, *Medical Research Fellow*[1], Grant Kiddle, *Orthopaedic Consultant*[2], Nigel Willis, *Orthopaedic Consultant*[2], John Carter, *Consultant Haematologist*[2], Mark Weatherall, *Statistician*[3], Richard Beasley, *Director, Respiratory Physician*[1,2]

[1]Medical Research Institute of New Zealand, Wellington, New Zealand,
[2]Capital and Coast District Health Board, Wellington, New Zealand
[3]University of Otago Wellington, Wellington, New Zealand

Key Words: Cast Immobilisation, Lower extremity, Venous thromboembolism, Pulmonary embolism, Deep vein thrombosis, intermittent compression

Word Count: Abstract (261) manuscript: (2,932), tables: 2, figures: 3

Short title: Foot pump compression, lower limb immobilisation and VTE prevention

Correspondence:

Dr Irene Braithwaite
Medical Research Institute of New Zealand
Private Bag 7902, Wellington 6242
New Zealand
Telephone: 64-4-805 0245
Fax: 64-4-389 5707
Email: Irene.braithwaite@mrinz.ac.nz

ABSTRACT

Objectives: To determine the likely enrolment rate of eligible participants into a randomised controlled trial (RCT) in which a within-cast intermittent pneumatic compression device using Jet Impulse Technology (IPC/JIT) is one of three possible interventions in a RCT for prevention of venous thromboembolism (VTE) in the clinical setting of isolated lower limb cast immobilisation.

Design: A prospective, open-label feasibility study of the IPC/JIT device placed within a lower limb cast.

Setting: Wellington Regional Hospital Fracture Clinic

Participants: Individuals aged 18 to 70 who presented with a lower limb injury requiring a minimum of four weeks below-knee cast immobilisation.

Intervention: Placement of an IPC/JIT device within lower limb cast.

Outcome measures: The main outcome measure was the proportion of eligible participants who participated in the feasibility study. Secondary outcome measures included adherence to device utilisation throughout the study, ease of application of the device and adverse events potentially associated with its use.

Results: The proportion of potentially eligible participants for the IPC/JIT device was only 7/142 (5%), 95% CI 2 to 9.9. Devices were used for a mean (range) of 4.1 (1.9 to 10.2) hours per day and none of seven participants had adequate adherence to the device. Three of the seven participants suffered an adverse event, including one DVT, one dorsal foot ulcer and one skin maceration.

Conclusions: A within-cast IPC/JIT device is unlikely to be a feasible randomisation arm for a RCT assessing possible interventions for the reduction of VTE risk in the clinical setting of lower limb injury requiring below knee cast immobilisation for a minimum of four weeks.

Trial registration: This trial was prospectively registered (ANZCTR 12615000192583 and was approved by the New Zealand Health and Disability Ethics Committees (14/STH/138/AM03).

STRENGTHS AND LIMITATIONS OF THIS STUDY:

This study is generalisable to all adults presenting with acute injury requiring lower limb cast immobilisation.

Data reflecting intermittent pneumatic compression device usage was downloaded directly from the machines and was not dependent on participant self-reporting.

Assessment of adverse events and VTE rates was limited by low recruitment into the study.

INTRODUCTION

Prolonged cast immobilisation of the lower limb after injury is associated with an increased risk of venous thromboembolism (VTE).[1–7] In a recent analysis of risk factors for VTE in two case-control studies, we found lower limb immobilisation was associated with a 73- fold increased risk of VTE.[8] Lower limb immobilisation was the most common potentially preventable cause of VTE in the 18 to 65 year age group, being present in one in seven cases.

A 2014 Cochrane review of low molecular weight heparin (LMWH) for prevention of VTE in patients with lower limb immobilisation reported a wide range, between 4.3% and 40%, for the incidence of VTE detected by radiological screening in patients in the control arms of these studies.[1] The risk of VTE was reduced by the administration of LMWH by approximately 50%. The risk reduction was similar in those with tendon ruptures compared to fractures, and for surgically compared to conservatively treated patients. Widespread use of LMWH could expose a potentially large patient group to the bleeding risks of its use and the American College of Chest Physicians (ACCP), in their Evidence-based Clinical Practice Guidelines on Prevention of Thrombosis (2012),[9] suggests that the risks and benefits of VTE prophylaxis are fairly evenly balanced and recommend no prophylaxis for cast immobilisation in isolated lower leg injuries distal to the knee. They also suggest that further research in this area is required.

In New Zealand LMWH for the prevention of VTE in the clinical setting of lower limb immobilisation is not funded for outpatients and its use has practical difficulties with patient adherence to a daily sub-cutaneous injection regime. Some evidence supports the use of low dose oral aspirin prophylaxis for VTE in a variety of medical and surgical patient groups.[10,11] A single large randomised placebo-controlled trial of low dose aspirin in hip fracture and elective arthroplasty found a one third reduction in VTE risk with only a small increase in post-operative bleeding.[12] There are no trials of low dose aspirin in lower limb immobilization. In an audit in our local

institution carried out after the introduction of aspirin 100mg daily for prophylaxis of VTE, we could identify no change in VTE rates. This suggests that aspirin is not an effective prophylactic measure in this clinical setting.[13] Oral anticoagulants including direct factor Xa inhibitors, such as rivaroxaban and apixaban, reduce the risk of VTE in total hip and knee arthroplasty with a favourable efficacy/risk profile compared with LMWH,[11,14] however their efficacy and safety profile in lower limb immobilisation is yet to be assessed.

The clinical effectiveness of intermittent pneumatic compression (IPC) systems in the prevention of DVT is well established as a non-pharmacological alternative for VTE prevention without the risk of bleeding.[9,15] Intermittent compression can be applied to the thigh, calf or foot, or any combination thereof, of a patient and has been used in both surgical and medical settings. IPC achieves an antithrombotic effect through increasing venous blood flow, thus reducing venous stasis, and also through stimulation of endogenous fibrinolysis.[16] Foot pumps, which we have shown increase popliteal vein flow within a lower limb cast[17] have proven efficacy in reducing VTE events in total knee replacement surgery, [18] and total hip arthroplasty.[19] Current recommendations for IPC include as adjunctive therapy to pharmaceutical anticoagulation, or in situations in which prophylactic anticoagulation is contra-indicated.[9]

We initially planned to undertake a three-arm, parallel groups, randomised controlled trial (proposed RCT) of low dose aspirin (100mg daily), an intermittent pneumatic compression (IPC) device plus low dose aspirin, or rivaroxaban (10mg daily) alone to prevent venous thromboembolism (VTE) secondary to cast immobility for a ruptured Achilles tendon or ankle fracture. However, when developing the details of the proposed RCT it became apparent there were no published trials of IPC devices in the setting of prolonged lower limb cast immobilisation. The potential for its use in this clinical situation was supported by our demonstration that IPC devices increase popliteal vein blood flow within a lower limb cast, [17]but this was in a study not exceeding one hour.

This current study was a feasibility study of the use of IPC technology in this instance, the VADOplex® VenaJet foot pump system marketed in New Zealand as Jet Impulse Technology (IPC/JIT) within lower limb casts. It aimed to estimate recruitment rates for a possible large-scale randomised controlled trial, the tolerability of IPC/JIT placement under a lower limb cast for a protracted period of time (a minimum of four weeks duration, with cast changes of up to two weeks apart), adherence to the proposed IPC/JIT in-cast regime, and adverse events potentially associated with its use. We were also interested in the proportion of potential participants who might not be eligible for recruitment to a trial arm that included the use of Rivaroxaban based on already using an oral anticoagulant, being at very high risk of VTE, being treated for active upper gastro-intestinal ulcer disease, immobility > 2 days prior to enrolment, significant liver disease, creatinine clearance <30ml/min), or concomitant use of HIV protease inhibitors.

PARTICIPANTS AND METHODS

Recruitment for the feasibility study occurred for six months, August 2015 to January 2016, with a further three months for follow-up of participants. Eligible participants were patients aged between 18 and 70 years presenting to Wellington Hospital Fracture Clinic with ruptured Achilles tendon, stable ankle fracture requiring a non-weight bearing cast, or, if possible, ankle fracture with operative fixation and then cast immobilisation. Exclusion criteria included patients with a high risk for VTE, active gastric or duodenal ulcer, already using anticoagulation, immobility >2 days before enrolment, significant liver disease (including moderate to severe hepatic impairment especially when associated with coagulopathy), renal impairment (estimated creatinine clearance <30ml/min), or concomitant use of HIV protease inhibitors.

Initially recruitment was limited to working hours however by the middle of September we identified that many potentially eligible participants presented on weekends, and so ethics approval was obtained at the end of September to extend recruitment over weekends, still within usual business hours of 8am to 5pm. Investigators and orthopaedic nursing staff identified potentially eligible participants, informed them about the open-label trial, and asked them if they would like to participate. Those who declined to participate were given the opportunity to provide a reason for non-participation, and if the reason for not participating was because the treatment was a device rather than a medication, this was documented. A record was kept of potential participants, including those who were treated and discharged outside of working hours, and of all potential participants approached during the working day. This record was used to identify the proportion of eligible participants likely to be recruited into the proposed RCT.

Potential participants were approached as they arrived in the outpatient department and were given a participant information sheet by the department nursing staff. If they expressed interest in the study, a study investigator was called to explain the study and to answer any queries potential participants had. Participants were advised that they had the ability to withdraw from the study at

any time. No study procedures were undertaken until after participants had signed written informed consent.

Participants who agreed to be enrolled into the feasibility trial had the IPC with Jet Impulse Technology (JIT) placed under their lower limb cast (Figure 1) and the usual care of aspirin EC 100mg daily was also prescribed. They were reviewed fortnightly at the fracture clinic for up to eight weeks. In-cast pad changes were planned at weeks two and four and possibly six depending on adherence of participants to the device and the treatment plans of the orthopaedic consultant. The IPC/JIT device was pre-set to inflate to 130mmHg once every minute, and participants had only to connect to the pump unit and turn the device on or off as required. To measure adherence with the device, participants were asked to use the IPC/JIT as much as possible while they were seated or immobile during the day and while in bed at night. Good adherence was defined as 60% of the total potential time available, namely 14.4 hours of a potential 24 hours per day. Total time, in hours, of IPC/JIT device usage was collected directly from the device at each clinic visit. To assess ease of application of the device and any adverse events, nursing staff completed a semi-structured record regarding the practicalities of device placement and related issues such as skin condition of the lower limb after removal of the cast at each clinic visit Adverse events and withdrawal reasons (if provided) were documented as they occurred.

The VADOplex® VenaJet foot pump system (OPED, Oberlaindern, Germany) is an intermittent pneumatic compression device that works with Jet Impulse Technology (JIT), to mimic the usual weight-bearing walking process. It comprises a 4.6kg, 320mm wide x 190mm high x 200mm deep (including mounting handle), bilateral pump unit, with an in-cast pad that is attached to the pump unit via an air tube (Figure 2). The pump mechanism mimics the natural full weight-bearing walking process, rapidly inflating a distal air-cell in the foot cuff to 130mmHg, which then settles to 52mmHg, followed by a proximal air-cell 0.3 seconds later, settling to 48mmHg. After 6 seconds of compression at 48 to 52mmHg, both air-cells deflate. This cycle is repeated every minute. The total

hours the device has been in use, both with the garment in operation, and without the garment, is indicated on the device readout. These numbers were documented at each visit.

All participants were scheduled for ultrasound examination of the popliteal to femoral vein of the affected limb (accessible above the leg cast) prior to each clinic visit, and again for ultrasound of the entire limb after removal of the cast or moonboot at the end of their orthopaedic treatment period which was expected to be between six and eight weeks. At any time between clinic visits and during the ensuing six week follow up period, if participants experienced signs or symptoms of DVT or PE, they would have an ultrasound or computed tomography pulmonary angiogram (CTPA) respectively, and be treated according to Wellington Hospital protocols. All participants were educated about the symptoms of DVT and PE and advised to seek medical review should these occur. A final follow up phone call was done six weeks after completion of cast-immobilisation treatment to ensure there had been no VTE event after completing the study.

Sample size and statistical methods

A total of 70 participants in the feasibility trial provided over 95% power to rule out a recruitment rate of less than 50%. It also provided 80% power with an alpha of 5% to rule out a complication rate of at most 33% if the anticipated complication rate was 10%; and to rule out adherence of less than 60% if the adherence rate was 75%. The main analyses planned were to estimate 95% confidence intervals proportions by the exact Clopper-Pearson method and to compare the achieved proportions with those outlined in the sample size calculation.

SAS version 9.4 was used.

RESULTS

The flow of potentially eligible participants is shown in Figure 3. Only 7/142 (5%) of potentially eligible participants were enrolled (Table 1), with an exact 95% CI of 2% to 9.9%, P-value for comparison with a rate of 50% <0.001. There were 58 (41%) potentially eligible participants who were not enrolled for logistics reasons; 39(27%) were admitted for operative intervention, and due to theatre logistics, could not be enrolled and 19 (13%) presented on weekends and evenings before the change in study protocol. There were 77 (54%) potentially eligible participants who were not enrolled due to reasons that were not anticipated at the time of design of the feasibility study, such as a moulded cast preventing the placement of the IPC/JIT, living out of geographical area thus making follow-up of participants impracticable, frailty of potential participants and use of a Plaster of Paris cast, the integrity of which might be impaired by the IPC/JIT device. Six potential participants declined due to the perceived impracticality of using the IPC/JIT device. There were no documented issues with skin integrity at initial device and cast placement. There were no issues with initial device placement by fracture clinic staff. A description of all 142 potential participants is shown in Table 2.

Table 1. Flow of potential participants through the feasibility study

Recruitment status, N=142	N (%)
Not enrolled – Logistic Reasons	**58 (40.8)**
- Operative intervention	39 (27.5)
- Weekend and evenings	19 (13.4)
Not enrolled – Other reasons	**77 (54.2)**
- Moulded cast	31 (21.8)
- Out of geographical follow up area	10 (7.0)
- Frailty	10 (7.0)
- Plaster of Paris cast – not suitable	9 (6.3)
Not enrolled – Due to exclusion criteria	**11 (8.2)**
- Injury >48 hours prior	8 (5.8)
- Weight bearing cast applied	2 (1.4)
- Other VTE risk factor	1 (1)
Declined study	**6 (4.2)**
Enrolled in study	**7 (5.0)**
Total	**142**

Table 2. Description of potential and enrolled participants in feasibility study

	Not recruited (N=135)	Recruited (N=7)
Continuous variables	**Mean (SD)**	
Age (years)	43.1 (15.0)	39.4 (7.9)
Categorical variable	**N (%)**	
Female	75 (56)	3 (43)
Ethnicity		
- European	87 (64.4)	2 (28.6)
- Maori	19 (14.1)	3 42.9)
- Pacific Island	11 (8.1)	2 (28.6)
- Asian	10 (7.4)	0 (0)
- Other	8 (5.9)	0 (0)
Day presenting		
- Monday	23 (17.0)	2 (28.6)
- Tuesday	19 (14.1)	1 (14.3)
- Wednesday	19 (14.1)	1 (14.3)
- Thursday	10 (7.4)	1 (14.3)
- Friday	22 (16.3)	1 (14.3)
- Saturday	27 (20.0)	0 (0)
- Sunday	15 (11.1)	1 (14.3)
Injury		
- Ankle Fracture	64 (47.4)	1 (15)
- Achilles tendon	42 (31.1)	6 (85)
- Fibula Fracture	13 (10.4)	-
- Other injury	16 (11.1)	-

Participants enrolled to use the IPC/JIT device

Of the seven participants enrolled in the feasibility study three participants did not complete the minimum four week period of IPC/JIT usage; one changed to a weight bearing cast after one week and the device was removed, one withdrew after developing an ulcer on the dorsum of their foot in the initial two week period, and one withdrew after two weeks due to maceration of the skin. Four participants completed four weeks of IPC/JIT device usage. One participant that completed the four week intervention had a DVT diagnosed at scheduled four week ultrasound, and was treated with rivaroxaban. No participants developed symptomatic VTE in the six week follow up period. Excluding the participant who changed to a weight-bearing cast the complication rate was 3/6 (50%) with 95% CI of 11.8 to 88.2; P-value for a comparison with 33% of 0.63.

Participant adherence to JIT and feedback about the device

The seven participants were issued the IPC/JIT devices and used the device for a total of 148 days. For these participants a total of 608 hours of use were recorded. The mean (range) of daily use was 4.1 hours (1.9 to 10.2). No participant met the proposed adherence target of an average of 14.4 hours per day in any of the two-week periods with a 95% confidence interval for adherence of 0 to 41%, P-value for comparison with 60%, 0.003. Of the seven participants, six did not use the device at night as it interfered with their sleep. All participants found the pump unit difficult to move around while they were non weight-bearing and on crutches, and tended to leave the pump unit in a single location where they were likely to spend most of their time. One participant attempted to take the pump unit to and from work, but found even with a backpack, that the pump unit was too large and awkward to carry around while on crutches. All participants indicated that they would use an IPC/JIT system again, but that the pump unit would have to be much smaller and lighter to allow ease of use.

Exclusion criteria for rivaroxaban arm of proposed RCT

Of the 142 potentially eligible participants identified in the study, 5 (3.5%) were already prescribed an anticoagulant, 3 (2.1%) had a high risk of VTE (two had active nephritis and one had a history of VTE) and 1 (0.7%) was on treatment for an active gastric ulcer. In all 9/142 (6.3%) would not have been eligible for Rivaroxaban treatment, 95% CI 2.9 to 11.7. None of the remaining 133 (91.7%) participants had any of the remaining exclusion criteria: immobility > 2 days prior to enrolment, significant liver disease, creatinine clearance <30ml/min) or concomitant use of HIV protease inhibitors.

DISCUSSION

This feasibility study shows that the IPC device utilising JIT technology is not a feasible randomisation arm in a RCT assessing VTE prevention rates in lower limb immobilisation. Furthermore, it is clearly not a therapeutic option for VTE prophylaxis in this clinical setting, regardless of its potential efficacy.

While our study was of the VADOplex® VenaJet foot pump system IPC/JIT device specifically, the findings in this study are broadly generalisable to individuals utilising IPC foot garments within rigid lower limb casts for prolonged periods in the outpatient community. The size and weight of the pump unit limiting patient mobility, interference with sleep leading to lack of use overnight, and skin related adverse events are likely to occur with other IPC systems in this clinical setting, thus impacting ongoing patient adherence and denying maximal antithrombotic effect.

It is interesting to compare outpatient utilisation of the IPC/JIT device when compared to studies of foot IPC use within hospital inpatient settings. In a study of patients after a total joint arthroplasty Pitto and Young reported that while 5% of patients discontinued IPC use between two and six days after initiation of use, foot pump devices had been used by the remaining 95% of patients for 15.9 hours daily.[20] Charalambous and colleagues assessed adherence to foot-pump usage in an inpatient setting after joint arthroplasty, and found that as patients got in and out of bed more frequently, their foot pumps were re-applied less often, and that only 60% of patients used foot pumps at night when confined to bed.[21] In our study, the IPC/JIT device was used for four hours/day and six of seven participants did not use the device at night. It is likely that in an unsupervised environment participants may be less likely to utilise the device, particularly overnight compared to an inpatient group. Adherence might be improved by utilising a smaller, more portable pump unit that was easier for participants to move around with. Providing more than one of the

current devices to each participant to allow placement at strategic locations at home or at work, while possible, is likely to prove too expensive.

It is informative to compare the complications associated with IPC/JIT use in this study with those experienced in other trials. Two out of seven (28.5%) participants suffered complications associated with the JIT device; one a dorsal foot ulcer and one who suffered skin maceration. This is higher than skin-related adverse events reposted in previous studies where dorsal ulcers, skin blisters and malleolar sores have been reported in 0% of 42 patients after hip surgery,[22] 6.7% of patients receiving plantar venous compression after total hip arthroplasty,[23] 4.5% in patients using a plantar compression device after total hip replacement[24] and 7.5% of patients using pre-operative plantar compression after ankle fracture.[25] Skin maceration is not uncommon within fibreglass casts, due either to excess sweating or inadvertent wetting of the cast, thus we were uncertain that the IPC/JIT device was the direct cause of the maceration. After this event, we started placing more protective material between the footpad and the skin and no further episodes occurred.

Foot pump devices have been shown to increase lower limb venous flow,[26–28] and a number of early studies have shown that foot pump prophylaxis with or without graduated compression stockings and/or pharmacological prophylaxis significantly reduces the risk of VTE after major orthopaedic surgery compared to; compression stockings alone,[29] or compression stockings and heparin.[23,24] These findings, in conjunction with the high rates of VTE found in the clinical setting of lower limb immobilisation,[1,13,30] raise the question of potential IPC/JIT prophylaxis in this situation, which would eliminate the risk of bleeding that exists with pharmacological prophylaxis. Since the inception of this feasibility study, Domeij-Arverud and colleagues[30] have published findings related to the use of an IPC and plastic foot cuff under a Plaster of Paris cast after Achilles tendon repair. They found that nine of 14 participants randomised to IPC treatment and six of 12 who received no intervention developed DVT during the intervention period. IPC malfunction and

the need to replace the cast correlated with a higher risk of VTE at 2 weeks resulting in the study being halted, suggesting that IPC prophylaxis in this clinical setting is no better than, and in fact is possibly worse than no prophylaxis. In our study, we enrolled only patients with fibreglass casts, there were no IPC/JIT malfunctions and no unscheduled cast changes were necessary. One in seven participants in our study was found to have a DVT on radiological screening, however given the small number of participants that utilised the IPC/JIT in this study, we cannot draw a conclusion about the likely VTE rates with this intervention.

If the randomised IPC/JIT treatment arm was dropped from the proposed RCT, and all the limiting logistics factors of the non-recruited group were suitably addressed e.g. full out of hours recruitment; access to the operating theatre post-operatively for device placement, about 130 patients would be eligible in each six month period. In this modified RCT, 200 participants would be required in each treatment arm (a total of 400) to ensure 90% power with an alpha of 5% to detect a 50% relative reduction in VTE events with rivaroxaban compared to the control arm (aspirin), assuming a 20% drop out rate. This suggests that the single Wellington Hospital site would have the potential to fully recruit the proposed RCT within a two year period, even if the recruitment rate was 80%.

Conclusions

The IPC/JIT device placed within a lower limb fibreglass cast is not a feasible randomisation arm for the proposed RCT investigating the rates of VTE in the clinical setting of outpatient temporary lower limb immobilisation due to low recruitment rates, poor adherence to treatment regimens and high rates of adverse events. The characteristics of potential participants suggest that recruitment into the rivaroxaban and aspirin arms of the proposed RCT from a single location is achievable.

STATEMENTS

Contributorship.

Study concept and design: R Beasley, I Braithwaite, M Weatherall, B De Ruyter, Grant Kiddle, Nigel Willis, John Carter. Acquisition of Data: I Braithwaite, B De Ruyter, A Semprini, S Ebmeier. Drafting of the manuscript: R Beasley, I Braithwaite. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: I Braithwaite, M Weatherall. Administrative, technical and material support: All authors. Study supervision: I Braithwaite.

Funding: The JIT devices were supplied by Dickson and Dickson Healthcare Ltd for the purposes of undertaking the study. The study was funded by the Health Research Council of New Zealand (HRC) through a feasibility grant (14/570), the first author was funded through the Health Research Council of New Zealand (HRC) by way of a Clinical Training Fellowship to undertake a PhD (14/040), and the Medical Research Institute of New Zealand also receives funding from the HRC through the Independent Research Organisations Capability Fund (14/1002). The funding parties had no involvement in the design or preparation of the study, collection, analysis and interpretation of the data, or the decision to submit for publication.

Competing Interests Statement: The authors have no competing interests to declare.

Guarantor: Dr I Braithwaite had access to all the data on the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the data being reported; that no important aspects of the analysis have been omitted; and that any discrepancies from the analysis as planned (and, if relevant, registered) have been explained

Data sharing statement: Patient level data available from the corresponding author on request. Consent was not obtained from participants for data sharing, but the presented data are anonymised and the risk of identification is low.

REFERENCES

1 Testroote M, Stigter W, de Visser DC, *et al.* Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization (review). *Cochrane Database Syst Rev* 2008;:CD006681.

2 Ettema HB, Kollen BJ, Verheyen CCPM, *et al.* Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. *J Thromb Haemost* 2008;**6**:1093–8.

3 Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N Engl J Med* 2002;**347**:726–30.

4 Lapidus LJ, Ponzer S, Elvin A, *et al.* Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. *Acta Orthop* 2007;**78**:528–35.

5 Lapidus LJ, Rosfors S, Ponzer S, *et al.* Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. *J Orthop Trauma* 2007;**21**:52–7.

6 Jorgensen PS, Warming T, Hansen K, *et al.* Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. *Thromb Res* 2002;**105**:477–80.

7 Kock HJ, Schmit-Neuerburg KP, Hanke J, *et al.* Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. *Lancet* 1995;**346**:459–61.

8 Braithwaite I, Healy B, Cameron L, *et al.* Lower limb immobilization and venous thromboembolism risk : combined case-control studies. *Submitted to JBJS* 2016.

9 Falck-Ytter Y, Francis CW, Johanson NA, *et al.* Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*;**141**:e278S – 325S.

10 Collins R, Baigent C, Sandercock P, *et al.* Antiplatelet therapy for thromboprophylaxis: the need for careful consideration of the evidence from randomised trials. Antiplatelet Trialists' Collaboration. *BMJ* 1994;**309**:1215–7.

11 Eriksson BI, Kakkar AK, Turpie AG, *et al.* Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *J Bone Jt Surg Br* 2009;**91**:636–44.

12 Rogers A (Pulmonary EPTCG. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;**355**:1295–302.

13 Braithwaite I, Dunbar L, Eathorne A, *et al.* Venous thromboembolism rates in lower limb immobilization after Achilles tendon injury unchanged after introduction of prophylactic aspirin: audit. *J Thromb Haemost* 2016;**14**:331–5.

14 Lassen MR, Ageno W, Borris LC, *et al.* Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty. *N Engl J Med* 2008;**358**:2776–86.

15 Niikura T, Lee SY, Oe K, *et al.* Incidence of venous thromboembolism in fractures around and below the knee with physical prophylaxis. *Orthopedics*;**35**:e1476–82.

16 Comerota AJ, Chouhan V, Harada RN, *et al.* The fibrinolytic effects of intermittent pneumatic compression: mechanism of enhanced fibrinolysis. *Ann Surg* 1997;**226**:306–13; discussion 313–4.

17 Braithwaite I, Mackintosh S, Buchanan S, *et al.* Venous haemodynamics of Jet Impulse Technology within a lower limb fibreglass cast : a randomised controlled trial (JIT in-cast trial). *Submitted to JRSM Open* 2015.

18 Wilson N, Das S, Maurice H, *et al.* Thrombosis prophylaxis in total knee replacement: does a simple mechanical method help? *Br J Surg* 1990;**77**:1417.

19 Fordyce MJF, Ling RS. A venous foot pump reduces thrombosis after total hip replacement. *J Bone Jt Surg [Br]* 1992;**74-B**:45–9.

20 Pitto RP, Young S. Foot pumps without graduated compression stockings for prevention of deep-vein thrombosis in total joint replacement: efficacy, safety and patient compliance. *Int Orthop* 2008;**32**:331–6.

21 Charalambous C, Cleanthous S, Tryfonidis M, *et al.* Foot pump prophylaxis for deep venous thrombosis - Rate of effective usage following knee and hip arthroplasty. *Int Orthop* 2003;**27**:208–10.

22 Asano H, Matsubara M, Suzuki K, *et al.* Prevention of pulmonary embolism by a foot sole pump. *J Bone Joint Surg Br* 2001;**83**:1130–2.

23 Bradley JG, Krugener GH, Jager HJ. The effectiveness of intermittent plantar venous compression in prevention of deep venous thrombosis after total hip arthroplasty. *J Arthroplasty* 1993;**8**:57–61.

24 Santori FS, Vitullo A, Stopponi M, *et al.* Prophylaxis against deep-vein thrombosis in total hip replacement. Comparison of heparin and foot impulse pump. *J Bone Jt Surg (B)* 1994;**76**:579–83.

25 Caschman J, Blagg S, Bishay M. The efficacy of the A-V Impulse system in the treatment of posttraumatic swelling following ankle fracture: a prospective randomized controlled study. *J Orthop Trauma* 2004;**18**:596–601.

26 Charles T, Mackintosh S, Fingleton J, *et al.* Efficacy of micromobile foot compression device in increasing lower limb venous blood flow. *Int J Vasc Med* 2013;**2013**:948769.

27 Delis KT, Slimani G, Hafez HM, *et al.* Enhancing venous outflow in the lower limb with intermittent pneumatic compression. A comparative haemodynamic analysis on the effect of foot vs. calf vs. foot and calf compression. *Eur J Vasc Endovasc Surg* 2000;**19**:250–60.

28 Morris RJ, Woodcock JP, Pitto RP, *et al.* Evidence-Based Compression. *Int Orthop* 2004;**239**:162–71.

29 Healy B, Beasley R, Weatherall M. Venous thromboembolism following prolonged cast immobilisation for injury to the tendo Achillis. *J Bone Jt Surg Br* 2010;**92**:646–50.

30 Domeij-Arverud E, Latifi A, Labruto F, *et al.* Can foot compression under a plaster cast prevent deep-vein thrombosis during lower limb immobilisation? *Bone Joint J* 2013;**95-B**:1227–31.

FIGURE LEGENDS

Figure 1. JIT/IPC footpad placement under lower limb cast

Figure 2. JIT/IPC device

Figure 3. Flow of participants through study

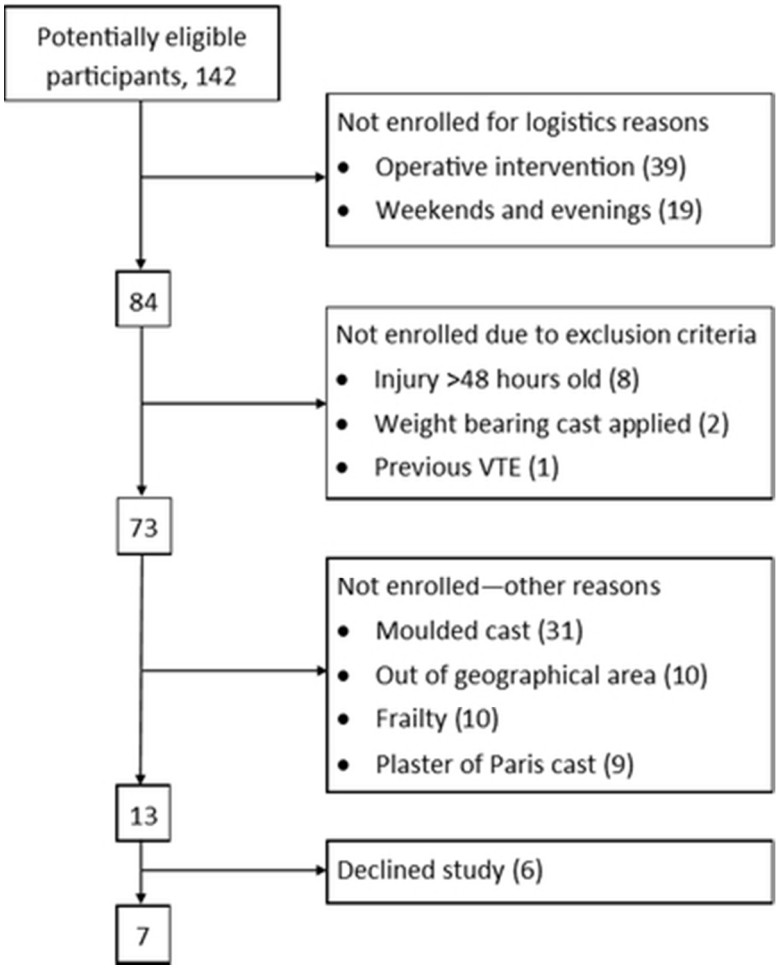
Figure 1. JIT/IPC footpad placement under lower limb cast

250x321mm (300 x 300 DPI)

Figure 2. JIT/IPC device

250x170mm (300 x 300 DPI)

Figure 1: Flow of eligible participants in study



Flow of participants through study

32x43mm (300 x 300 DPI)