The Clots in Legs Or sTockings after Stroke (CLOTS) 3 trial: a randomised controlled trial to determine whether or not intermittent pneumatic compression reduces the risk of post-stroke deep vein thrombosis and to estimate its cost-effectiveness

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Scientific summary

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Scientific summary

Background

Patients admitted to hospital with a stroke of recent onset are at risk of developing deep vein thrombosis (DVT) which may be complicated by pulmonary emboli (PEs) and sudden death. The risk of DVT is highest in patients who are initially immobile; among these patients, it may affect about 20% within the first few weeks of stroke. Prophylactic anticoagulation reduces the frequency of DVTs (mostly asymptomatic and detected only by scanning the leg veins), but increases the risk of major bleeds, perhaps explaining why randomised trials have not shown any improvement in either survival or functional outcomes in survivors. Furthermore, we have previously shown that, after stroke, graduated compression stockings are not effective for the prevention of DVT and PE. Intermittent pneumatic compression (IPC) has been shown to reduce the risk of DVT in patients undergoing surgery but has not been robustly evaluated in hospitalised medical patients, including those with stroke.

Objectives

To determine whether or not:

(a) IPC applied to the legs of immobile stroke patients admitted to hospital reduces their risk of proximal DVT
(b) IPC reduces the risk of any (proximal or calf vein, symptomatic or asymptomatic) DVTs, PEs or deaths within the 30-day treatment period
(c) IPC increases the risk of skin breaks, falls or fractures within the 30-day treatment period
(d) IPC use is associated with reductions in venous thromboembolism (VTE) or improvements in survival, function or quality of life over the first 6 months after stroke
(e) IPC use influences NHS hospital costs and to determine its cost-effectiveness in stroke patients.

Methods

Design overview

The Clots in Legs Or sTockings after Stroke (CLOTS) 3 trial is a multicentre, parallel-group trial with a centralised randomisation system to allocate treatments in a 1 : 1 ratio, which ensures allocation concealment. It enrolled consenting patients in 94 centres in the UK, from day 0 to day 3 of admission and allocated them, via the central randomisation system, to IPC or no IPC.

Setting and participants

Between December 2008 and September 2012 we enrolled 2876 patients in 94 hospitals in the UK and completed follow-up in March 2013. Patients were eligible for inclusion if they were admitted to hospital within 3 days of an acute stroke (ischaemic or haemorrhagic); patients could be enrolled between the day of admission (day 0) and day 3 in hospital, and if they were immobile (i.e. unable to walk independently to the toilet). We excluded patients with subarachnoid haemorrhage and those with severe peripheral vascular disease, congestive heart failure or skin lesions on the legs which precluded the use of IPC.

Randomisation and interventions

Having obtained consent, the clinician entered a patient's baseline data into our computerised central randomisation service via a secure web interface. Once the computer program had checked these baseline data for completeness and consistency, it generated the patient's treatment allocation: either 'routine care plus thigh-length IPC' or 'routine care and no IPC'.

In patients allocated to IPC, nursing staff applied the Kendall SCD™ express sequential compression system (Covidien Ltd, Mansfield, MA, USA) with thigh-length sleeves, in accordance with the manufacturer's instructions, to both legs. It was worn day and night for 30 days or until a second-screening compression duplex ultrasound (CDU) had been performed (if after 30 days) or until the patient was independently mobile, was discharged from the randomising hospital or refused to wear the sleeves or the staff became concerned about the patient's skin. We stipulated that both treatment groups should receive the same routine care that could include, depending on local protocols, early mobilisation, hydration and antiplatelet or anticoagulant drugs.

Outcomes and follow-up

The primary outcome was the occurrence of either a symptomatic or an asymptomatic DVT in the popliteal or femoral veins (detected on the first or second CDU performed as part of the trial protocol), or a symptomatic DVT in the popliteal or femoral veins, confirmed on imaging (either CDU or venography), within 30 days of randomisation. Secondary outcomes included death, any DVT or PE, skin breaks and falls with injuries or fractures and duration of IPC use within 30 days and any DVT or PE, survival, functional status [as measured by the Oxford Handicap Scale (OHS)] or quality of life [as measured by the European Quality of Life-5 Dimensions 3 Level (EQ-5D-3L) questionnaire] at 6 months.

Data collection methods

We aimed to perform CDU of the veins of both legs between 7 and 10 days after randomisation in all patients and, whenever practical, obtained a second CDU scan between day 25 and day 30. The local co-ordinator reviewed the medical records and extracted the information needed to complete our discharge form. We could not blind the local co-ordinator to group allocation. The discharge form included checkboxes to record the secondary outcomes and adverse events.

Approximately 6 months after randomisation, we sent a postal questionnaire to each patient's general practitioner to establish the patient's vital status and the occurrence of DVTs or PEs since hospital discharge. We followed up surviving patients 6 months after enrolment by postal questionnaire; the chief investigator (MD) interviewed non-responders by telephone, blind to treatment allocation. The questionnaire included items related to a patient's living circumstances, disability (OHS) and health-related quality of life (EQ-5D-3L).

Statistical analysis

We estimated that we would need 2800 patients to provide 90% power ($\alpha = 0.05$) to identify a 4% absolute reduction in our primary outcome (i.e. 12% to 8%).

For the purposes of all analyses, we retained participants in the treatment group to which they were originally assigned. We calculated the absolute difference in proportion of patients with an outcome between groups and the 95% confidence intervals (CIs). We compared the proportion with primary or secondary outcomes with odds ratios (ORs) and 95% CIs adjusted with logistic regression for the four variables included in our minimisation algorithm (predicted stroke outcome, delay from stroke onset to randomisation, ability of the patient to lift both legs off the bed and use of anticoagulants or alteplase).

Economic analyses

Economic analysis of trial treatment effects involved a within-trial evaluation of cost-effectiveness. A NHS hospital perspective was adopted for assessing resource use and costs. Patient-specific hospital resource was measured using the duration of stay for the index episode following randomisation.

Ethics and consent

The protocol was approved by the Scotland A Multicentre Research Ethics Committee (08/MREC00/73) and the Newcastle and North Tyneside 1 Research Ethics Committee for England (08/H0906/137). The study was jointly sponsored by the University of Edinburgh and NHS Lothian.

Role of the funding sources

The funders of the study, including Covidien Ltd, had no role in data collection, storage or analysis, drafting of this report or the decision to publish. We allowed them to comment on the draft manuscript prior to final submission.

Results

Between 8 December 2008 and 6 September 2012, 2876 patients were enrolled in 94 centres in the UK and an additional 11 centres took responsibility for delivering the allocated treatment and follow-up for patients who were transferred from the randomising hospitals. Of the 2876 patients enrolled, 1438 were randomly assigned to receive IPC and 1438 to receive no IPC. The patients' baseline characteristics were well balanced between treatment groups. Use of antiplatelet medication and prophylactic-dose heparin or low-molecular-weight heparin after randomisation was very similar in both treatment groups. The mean duration of IPC use was 11.7 days [standard deviation (SD) 10.6 days] and the median duration was 8 days [interquartile range (IQR) 3–20 days]. Perfect adherence was achieved in 378 (26.3%) of the 1438 patients in the IPC group. The mean adherence was 55.6% (SD 38.5%) and the median adherence was 55.5% (IQR 16.7–100%).

The primary outcome occurred in 122 (8.5%) of the 1438 patients allocated to IPC and in 174 (12.1%) of the 1438 patients allocated to no IPC, giving an OR of 0.65 (95% CI 0.51 to 0.84; $p = 0.001$) after adjustment for baseline variables. The absolute risk reduction was 3.6% (95% CI 1.4% to 5.8%). The primary outcome was confirmed in 276 (93%) of the 296 patients by central review of the CDU images and in the remaining 20 (7%) patients by the local clinical radiologist's report of the CDU. To allow for any observer bias in detecting symptomatic DVTs not detected on routine screening CDU, we repeated the primary analysis excluding those primary outcomes where a DVT was suspected before the CDU ($n = 22$). The estimates of effect were unchanged. In our prespecified subgroup analyses, we noted no significant interactions between any of the subgroups and the effect of treatment on the primary outcome.

For the secondary outcomes, there were significant reductions in the outcomes of any (symptomatic or asymptomatic involving proximal or calf veins) DVT [IPC, $n = 233$ (16.2%), vs. no IPC, $n = 304$ (21.1%); OR 0.72, 95% CI 0.60 to 0.87] and symptomatic (including proximal or calf) DVT [IPC, $n = 66$ (4.6%), vs. no IPC, $n = 90$ (6.3%); OR 0.72, 95% CI 0.52 to 0.99]. In some patients, calf veins could not be visualised fully: the first CDU was unable to exclude an isolated calf DVT in 615 (47%) of 1315 patients in the IPC group and in 596 (46%) of 1305 patients in the no-IPC group. Among patients in whom CDU was repeated, we were unable to exclude an isolated calf DVT in 453 (47%) of 955 patients in the IPC group and in 451 (48%) of 938 patients in the non-IPC group. Patients allocated to IPC had significantly more skin breaks than patients allocated to no IPC [IPC, $n = 44$ (3.1%), vs. no IPC, $n = 20$ (1.4%); OR 2.23, 95% CI 1.31 to 3.81]. The risk of falls with injury [IPC, $n = 33$ (2.3%), vs. no IPC, $n = 24$ (1.7%); OR 1.39, 95% CI 0.82 to 2.37] or fractures [IPC, $n = 4$ (0.3%), vs. no IPC, $n = 4$ (0.3%)] within 30 days did not differ between groups. However, the reporting of these secondary outcomes and adverse effects in hospital was based on case note review and was not masked to treatment allocation. These data for adverse events are therefore prone to ascertainment bias. We noted non-significantly fewer deaths from all causes within 30 days among those allocated to IPC than among those allocated to no IPC [IPC, $n = 156$ (10.8%), vs. no IPC, $n = 189$ (13.1%); OR 0.80, 95% CI 0.63 to 1.01]. The Cox proportional hazards

model, adjusted for the factors included in our minimisation algorithm, showed a reduced probability of death up to 6 months after randomisation in those allocated IPC with a hazard ratio of 0.86 (95% CI 0.74 to 0.99; $p = 0.042$).

At 6 months, there were no statistically significant differences in patients' functional status or quality of life. There was no significant gain in quality-adjusted survival. The direct cost of preventing a DVT was £1282 (95% CI £785 to £3077). We found no evidence of an excess of DVTs or PEs in the post-treatment period to indicate that IPC simply deferred events.

Conclusions

The CLOTS 3 trial has shown that IPC applied to immobile stroke patients soon after admission to hospital significantly reduces the risk of proximal DVT, symptomatic DVTs and any DVTs including those affecting the calf. We were unable to demonstrate a statistically significant reduction in PEs. Although there was a significant excess of skin breaks and a non-significant excess of falls with injury, the absolute risk of these adverse events was low, and most adverse events were not clearly attributable to the IPC. Fewer patients allocated to the IPC group died (both within 30 days and up to 6 months after randomisation) than died in the no-IPC group, although these differences were not statistically significant. However, a more sensitive and prespecified analysis of the hazard of death within the first 6 months, adjusted for baseline covariates, demonstrated that the relative hazard of death was reduced by about 14%, which was statistically significant ($p = 0.042$).

Further research is needed to evaluate the effectiveness of IPC in other groups of hospitalised medical patients at high risk of VTE and, ideally, to show whether or not IPC reduces deaths from all causes as it appears to do after stroke in the CLOTS 3 trial. In addition, under trial conditions, adherence to IPC was modest and it is likely that this reduced the size of the effect observed. Research into methods to improve adherence to IPC might provide information which would increase the benefits of IPC in stroke patients.

Trial registration

This trial is registered as ISRCTN93529999.

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This report

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