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Does this recent randomised controlled trial of intermittent pneumatic compression devices really indicate that they are ineffective in critical care patients?

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Provenance: This is an invited Editorial article by the Section Editor Xue-Zhong Xing [National Cancer Center (NCC)/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China].

Comment on: Arabi YM, Al-Hameed F, Burns KEA, *et al.* Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. *N Engl J Med* 2019;380:1305-15.

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Arabi *et al.* (1) reported the results of their multicentre, international randomised controlled trial (RCT) (ISRCTN44653506) of adjunctive Intermittent Pneumatic Compression (IPC) for Venous Thromboprophylaxis in *N Engl J Med* in Feb 2019.

Their purpose was to reliably establish whether IPC in critically ill patients receiving pharmacologic thromboprophylaxis [heparin/low molecular weight heparins (LMWH)] would result in a lower incidence of deep vein thrombosis (DVT) than heparin/LMWH alone.

Within 48 hours of admission to a critical care unit they randomly assigned adult patients to heparin/LMWH plus IPC for ≥ 18 hours each day (intervention) or heparin/LMWH alone (control). The primary outcome was a new proximal DVT, detected on compression Duplex ultrasound (CDU) of the deep veins of the legs, carried out twice a week, starting on day three after randomization until discharge from critical care, death, recovery of mobility, or four weeks after randomisation, whichever occurred first.

They randomised 2,003 patients, 991 were randomised to the intervention (IPC) arm and 1,012 to the control arm. Adherence was reasonable, IPC was worn for a median of 22 hours per day for a median of 7 days. A proximal DVT was identified in 37 of 957 (3.9%) in the IPC arm and in 41 of 985 (4.2%) in the control arm [risk ratio (RR) =0.93; 95% confidence interval (CI), 0.60 to 1.44; P=0.74]. Pulmonary embolism (PE) or any DVT was detected in 103 of 991

(10.4%) in the IPC arm and in 95 of 1,012 (9.4%) in the control arm (RR =1.11; 95% CI, 0.85 to 1.44), and death from any cause at 90 days occurred in 258 of 990 (26.1%) in the IPC arm and 270 of 1,011 (26.7%), in the control arm (RR =0.98; 95% CI, 0.84 to 1.13).

The authors concluded that in patients in critical care who were receiving heparin/LMWH, the use of IPC did not significantly reduce the risk of venous thromboembolism or death compared with heparin/LMWH alone.

As the lead for the CLOTS trials collaboration, I was personally surprised by this result. In 2013, we reported the results of the CLOTS3 trial (ISRCTN93529999) (2). We aimed to determine if IPC reduced the risk of DVT, PE and death in immobile stroke patients admitted to hospital in the UK. The background to the CLOTS3 trial was that DVT, PE and related deaths were regarded as important complications in patients hospitalised with severe stroke (3,4). However, previous trials, including a trial of almost 20,000 patients had shown that whilst prophylactic heparin might reduce the risk of DVT and PE, it increased the risk of bleeding, and had no net benefit (5,6). Subsequent individual patient data meta-analyses could not identify any specific subgroup of stroke patients who might benefit from prophylactic heparin (7). Also, trials had demonstrated that graduated compression stockings did not reduce the incidence of DVT in immobile stroke patients (8). A systematic review of RCTs in patients undergoing surgery

had suggested that IPC reduced the risk of DVT (9). The CLOTS3 trial was a multicentre parallel group RCT assessing IPC in immobile patients with acute stroke. We recruited patients from day 0 to day 3 of admission and randomised them to receive IPC or no IPC on a background of normal care. A technician who was masked to treatment allocation performed a CDU 7 to 10 days and, wherever practical, 25 to 30 days after randomisation. Patients were followed for 6 months to detect later symptomatic VTE and deaths. The primary outcome was proximal DVT on a screening CDU or any symptomatic DVT in the proximal veins, confirmed on imaging, within 30 days of randomisation. Patients were analysed according to their treatment allocation. We enrolled 2,876 immobile stroke patients in 94 centres in the UK. A proximal DVT was detected in 122 (8.5%) of 1,438 in the IPC arm and 174 of 1,438 (12.1%) in the no IPC arm; an absolute reduction in risk of 3.6% (95% CI, 1.4 to 5.8) [adjusted risk ratio 0.69 (95% CI, 0.55 to 0.86); $P=0.001$]. Survival to 6 months was significantly better in the IPC arm [hazard ratio 0.86 (95% CI, 0.74 to 0.99), $P=0.042$]. We concluded that IPC was effective in reducing the incidence of DVT and possibly improving survival in patients who are unable to walk independently after stroke.

There are no definite explanations for these apparently divergent results. Both trials were methodologically similar and quite robust. However, compared with CLOTS3, Arabi *et al.* did not attempt to mask those carrying out the CDUs which could have led to some expectation bias. However, this would generally be expected to lead to an over estimate of treatment effect. Also, their follow up protocol, although intensive with frequent scanning, was dependent on patients' length of stay in critical care. Ideally, in RCTs follow up is to a fixed time point after randomisation, and will therefore be similar in the two arms. However, there was little difference in the actual duration of follow up between the two arms.

There are other differences between the trials. This trial included a far more heterogeneous group of patients in terms of their underlying condition—most were admitted with medical problems—few were post-surgical or had stroke.

In critical care prophylaxis with heparin/LMWH is recommended for those judged to be at low bleeding risk. In ischaemic stroke, prophylaxis with heparin/LMWH is far more controversial. Previous meta-analyses of trials of heparins/LMWH in medical patients, including those with stroke ($n=36,122$) have shown significant reductions

in pulmonary emboli (three in 1,000, 95% CI, 1 to 3), but only non-significant reduction in deaths (six in 1,000, 95% CI, 0 to 11), perhaps partly because any reduction in major VTE was offset by a significant increase in major bleeds (four in 1,000, 95% CI, 1 to 7) (10,11). Interestingly, studies in critical care mirror these data (12). In this trial heparin/LMWH was given to all of the patients whereas in CLOTS3 only 21.5% received anticoagulation or alteplase—this might contribute to the lower rate of proximal DVT (3.9%) and VTE (9.9%) within 28 days compared with the CLOTS3 trial (10.3%, 19.9% respectively within 30 days).

The sample size of this trial was based on an expected absolute risk reduction of 3% from an expected proximal DVT rate of 7% in the control arm to 4%, but the actual risk was 3.9% across the arms. Therefore, the trial had much less power than predicted. The 95% CI of their result (95% CI, 0.60 to 1.44), includes the point estimate from the CLOTS 3 trial (0.69), so they may simply have been underpowered and unlucky, and failed to identify an effect similar to that seen in CLOTS3.

A subgroup analysis of CLOTS3 based on the baseline use of alteplase or anticoagulants showed no significant interaction with the effect of IPC, however this subgroup analysis was underpowered. Given that anticoagulation and IPC are presumed to be working on two different sides of Virchow's triad, I find it difficult to imagine that the presence of anticoagulation would negate the effectiveness of IPC. However, because of the reduced incidence of VTE with anticoagulation, this would make the effect more difficult to demonstrate in a randomised trial because the event rates would be lower.

Both trials used IPC, but in CLOTS3 all patients had thigh-length compression delivered by a single device (Covidien SCD Express system) which delivered, sequential, circumferential compression at a frequency determined by the rate of venous refill. Arabi *et al.* took a more pragmatic approach and did not specify the type of IPC. Only 18.7% delivered thigh-length compression, with the remainder providing either calf only or foot compression. A range of devices will have provided different types of compression. There have been no reliable trials to indicate whether the type of compression (thigh *vs.* calf *vs.* foot; single or sequential, circumferential or other, fast or slow, fixed or variable frequency) impacts on the effectiveness in reducing the risk of VTE, but different manufacturers justify their approaches on the basis venous flow rates.

In conclusion, the neutral result presented by this trial is

unexpected. Given the strong evidence that IPC is effective in peri operative patients and those with stroke I wonder whether lack of sufficient statistical power and perhaps the type of IPC used might explain their result. I think it would be justified to carry out a larger RCT, testing thigh-length, sequential IPC in a broad range of high-risk critical care patients with and without pharmacological prophylaxis before concluding that IPC is ineffective.

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None.

Footnote

Conflicts of Interest: M Dennis received departmental funding from the National Institute for Health Research Health Technology Assessment Boards to run the CLOTS 3 trial. Covidien provided compression equipment to the sites participating in the trial. M Dennis has no personal interest in Covidien and has never accepted any funding, grants or speakers fees from them.

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