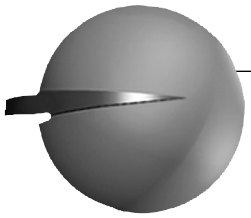

Evidence Review

Effect of Intermittent Pneumatic Compression on Preventing Deep Vein Thrombosis Among Stroke Patients: A Systematic Review and Meta-Analysis

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Keywords
stroke, deep vein thrombosis, intermittent pneumatic compression, meta-analysis

ABSTRACT

Background: Deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE) are common complications of stroke. However, the effect of intermittent pneumatic compression (IPC) for patients after stroke is uncertain.

Objectives: To assess the effectiveness and safety of IPC in reducing the risk of DVT, PE, and mortality in stroke patients.

Methods: We searched leading medical databases including Medline, EMBASE, Cochrane Library, Wanfang, CNKI, and CBM, from inception to June 2, 2017. Studies comparing IPC with no IPC in stroke patients were included. Agreement was measured using simple agreement and kappa statistics. The rates of PE, DVT, and mortality were compared. The results were pooled using a fixed effects model to evaluate the differences between the IPC and control groups. If there was significant heterogeneity in the pooled result, a random effect model was used.

Results: We identified seven randomized controlled trials that included 3,551 stroke patients. The average calculated κ for the various parameters was $\kappa = 0.96$ (0.70–1). Overall, IPC significantly reduced the incidence of DVT in stroke patients (risk ratio [RR] = 0.50; 95% confidence interval [CI 0.27, 0.94]). At the same time, IPC increased IPC-related adverse events (RR = 5.71; 95% CI [3.40, 9.58]). Though IPC was associated with a significant increase in survival by 4.5 days during 6 months of follow-up (148–152 days; 95% CI [–0.2, 9.1]), there was a mean gain of only 0.9 days (26.7–27.6 days; 95% CI [2.1, 3.9]) in quality-adjusted survival during the 6-month follow-up. Overall, sensitivity analyses did not alter these findings.

Linking Evidence to Action: This review provides an important basis for preventing DVT in stroke patients, especially in hemorrhagic stroke patients. IPC significantly reduces the risk of DVT and significantly improves survival in a wide variety of patients who are immobile after stroke. However, IPC does not significantly improve quality-adjusted survival. Clinicians should take functional status and quality of life into consideration when making decisions for stroke patients.

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are known to be the most important, preventable event among hospitalized patients (Dennis, 2013). Patients after stroke who have significant weakness of the leg or are immobile appear to be at great risk. Evidence shows that 40% of stroke patients appear to demonstrate DVTs in the first three weeks and above-knee DVT accounts for 18% of DVTs (Dennis, 2013). Clinically evident PE varies from 1% to 30%. The prevention techniques for DVT in stroke patients include mechanical thromboprophylaxis and pharmacological thromboprophylaxis. Though there is evidence showing that the use of anticoagulation in patient after acute stroke significantly reduces the incidence of DVT (with a risk reduction 54–71%; Naccarato, Chiodo Grandi, Dennis, & Sandercock, 2010), its benefit was offset by extracranial hemorrhages. The overlap of factors that predict venous thrombosis with those that predict bleeding risk resulted in the underuse of anticoagulation and the high risk of DVT in patients who were not treated with anticoagulation in a timely fashion.

Due to the uncertainties about the net benefit of anticoagulation for patients after stroke, interest in mechanical thromboprophylaxis to prevent DVTs has increased. Intermittent pneumatic compression (IPC), as one part of mechanical thromboprophylaxis, includes inflatable sleeves that can be applied to the calf, thigh, or both. IPC was thought to reduce

the risk of venous thrombosis by increasing the flow of venous blood, stimulating release of intrinsic fibrinolytic factors, and reducing stasis (Dennis, 2013). A meta-analysis in 2013 included 70 trials involving 16,164 hospitalized patients. It concluded that IPC therapy was more effective than no IPC prophylaxis in reducing DVTs (risk ratio [RR] = 0.43; 95% confidence interval [CI 0.36, 0.52]; $p < .01$; $I^2 = 34\%$) and that IPC can be as effective as pharmacological thromboprophylaxis (Ho & Tan, 2013). However, there were only 383 acute stroke patients in the study (Ho & Tan, 2013), and the vast majority of the included patients were surgical or with malignant disease. The pooled results were not generalizable to patients after stroke.

A systematic review (Naccarato et al., 2010) published in the Cochrane Library identified two trials including 177 stroke patients and reported on the effect of IPC versus no IPC therapy. The review showed that IPC produced a nonsignificant reduction in the risk of DVTs (OR = 0.45; 95% CI [0.19, 1.10]). However, recent results from a multicenter randomized controlled trial (RCT) including 2,876 stroke patients showed that IPC was associated with an absolute risk reduction of 3.6% (95% CI [1.4, 5.8]). The net effect of IPC for stroke patients remains contentious. In this meta-analysis, we assessed the effect of IPC on the risk of DVTs, PE, and mortality compared with no IPC prophylaxis.

METHODS

Literature Search

We systematically searched the following six published medical databases: Medline, EMBASE, Cochrane Library, Wanfang, CNKI, and CBM from inception to June 2, 2017. During the electronic database search, the following medical subject headings terms or keywords were used to generate sets for themes: "prevention"; "IPC"; "deep vein thrombolism"; "DVT"; "stroke patients"; or "PE." We manually screened reference lists from review articles and identified trials to identify relevant studies, but we did not find additional references. No language restrictions were used. The searches were limited to studies performed in humans.

Study Inclusion Criteria and Exclusion Criteria

We included clinical trials of IPC for stroke patients that reported outcomes of deep vein thromboembolism, PE, mortality, and IPC-related adverse events. Studies were included if they met the following criteria: (a) were RCTs, (b) included stroke patients who received IPC, (c) included patients in a control group did not receive IPC, (d) included adult patients aged ≥16 years, and (e) were original papers. Studies were excluded if they met following criteria: (a) were animal studies, mechanistic studies, case reports, editorials, comments, guidelines and review articles; and (b) did not report DVT as an outcome.

Outcome Measures

Our primary outcomes were as follows: (a) the incidence of DVT, (b) IPC-related adverse events, and (c) 6-month survival. The secondary outcomes were the rate of death and PE proved by ventilation or perfusion (V/Q) scan, conventional arteriogram, or computed tomography.

Study Selection

Two reviewers (Dongdong Zhang and Fenfen Li) independently evaluated the identified 282 studies for their eligibility to be included in a nonblinded fashion. Only RCTs of IPC versus no IPC were included. All papers that met the inclusion criteria by abstract and title were reviewed as full-texts. Inconsistencies were resolved by discussion or consulting a third reviewer (Ganqin Du). A preferred reporting item for systematic reviews and meta-analyses (PRISMA) flow diagram was used to summarize the study selection process (Figure S1).

Data Extraction

All relevant data, including author, year, type of publication, patient population (sample size, gender, age), study design, and desired clinical end points (incidence rate of DVT, PE, mortality, and IPC-related adverse events) were extracted. We made attempts to contact the authors of the studies to obtain pertinent missing data. Data extraction was conducted independently by two authors (Dongdong Zhang and Fenfen Li) using a standardized data abstraction form, and consensus was achieved for all data. Interinvestigator reliability was assessed using kappa statistics for risk of biased assessment.

Quality Assessment

The quality of each included study was assessed using the Cochrane risk of bias tools for RCTs (Higgins et al., 2011). We assessed the following methodological features most relevant to the control of bias: random sequence generation; random allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other bias (Bischoff-Ferrari et al., 2005). The risk of bias in each domain is graded as high, low, or unclear.

Statistical Analysis

The outcomes including DVT, PE, and mortality were dichotomous variables. We used Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for the statistical analysis. Because outcomes including DVT, PE, and mortality were rare events and some trials were small, the Mantel–Haenszel method was chosen (Salliot, Dougados, & Gossec, 2009). Where appropriate, we calculated RRs for dichotomous outcomes (e.g., IPC-related adverse events, mortality, and incidence of DVT) in a Mantel–Haenszel fixed effect model and 95% CIs for the pooled outcome.

Heterogeneity among studies was assessed by the Cochran Q test ($p < .1$; Egger, Juni, Bartlett, Holenstein, & Sterne, 2003; Feit et al., 2000) and the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance (low heterogeneity: <25%,

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moderate heterogeneity: 25–75%, and high heterogeneity: >75%; Higgins & Thompson, 2002). If heterogeneity was found among studies, a Mantel–Haenszel random-effects model was used to pool overall outcomes. Prespecified subgroup analyses were performed by dividing the included population into hemorrhagic stroke and ischemic stroke groups, 24 hr of continuous use or intermittent use groups, within 72 hr after stroke or more than 72 hr after stroke groups.

The findings of a meta-analysis can be influenced by a single outlier study or a large study. A sensitivity analysis was conducted to assure that the results were not influenced by a single study by (a) excluding outlier studies and (b) excluding the largest study.

RESULTS

Search Results

We identified 282 citations (Figure 1) published between September 7, 1982 and June 2, 2017 from Cochrane, EMBASE, Medline, Wanfang, and CNKI. After de-duplication and initial review, we excluded 252 articles. Of the remaining publications, 30 studies were viewed in detailed full text. A total of seven RCTs met the eligibility criteria.

Study Characteristics

We identified seven RCTs (Dai, 2015; Dennis, 2013; Lacut et al., 2005; Pambianco, Orchard, & Landau, 1995; Prasad, Banerjee, & Howard, 1982; Wan, Huang, Lv, Tian, & Wang, 2013; Wang, 2017) that tested the effect of IPC on DVT outcomes in stroke patients. All included studies were conducted between 1982 and 2017 with a total of 3,551 stroke patients from four countries including the United States (one trial), France (one trial), China (three trials), and the United Kingdom (two trials). Study size ranged from 26 to 2,876. The included studies were reported in English (four trials) and Chinese (three trials). Three trials by Dennis (2013), Pambianco et al. (1995), and Wan et al. (2013) studied the effects of IPC in preventing DVT for ischemic stroke patients versus no IPC. Similarly, four trials (Dai, 2015; Dennis, 2013; Lacut et al., 2005; Wang, 2017) included hemorrhagic stroke patients and studied the effect of IPC in preventing DVT versus no IPC. According to the method of IPC used, the included patients were divided into 24-hr continuous use and intermittent use. The detailed characteristics, method of detecting DVT, study design, and outcomes of the included trials are described in Table S1.

OUTCOMES

Effect of IPC on Risk of DVT Compared With No IPC

Data on DVT were available in seven RCT studies with 3,551 patients. There was moderate heterogeneity among the studies and a Mantel–Haenszel random effect model was used to pool the summary outcome ($p = .03$; $I^2 = 58\%$). The pooled result showed that IPC was more effective than no IPC prophylaxis in reducing DVT (seven trials 7.9% vs. 12.6%; absolute risk reduction 4.7%; RR = 0.50; 95% CI [0.27, 0.94]; $p = .03$; $I^2 = 58\%$; Figure S2). After excluding trials for which there were treatment measures in the control group such as pharmacological therapy (Dai, 2015; Wang, 2017) and elastic stockings (ES) physical therapy, in three trials (Dennis, 2013; Pambianco et al., 1995; Prasad et al., 1982) that directly compared IPC and no IPC alone, IPC was associated with a reduced risk of DVT (RR = 0.74; 95% CI [0.60, 0.91]; $p = .004$; $I^2 = 0\%$). Upon removing the largest trials (Dennis, 2013) to assess if it had undue influence, the results were unchanged (RR = 0.35; 95% CI [0.13, 0.99]; $p = .05$; $I^2 = 68\%$).Thus, the results of a sensitivity analysis support the inclusion of all studies in the meta-analysis.

Mortality

Of the 3,053 patients in the three trials (Dennis, 2013; Lacut et al., 2005; Prasad et al., 1982) that reported on mortality, 1,525 received IPC therapy and 1,528 were allocated to the control group. The incidence of mortality was 10.75% (164/1,525) in the IPC group and 12.89% (197/1,528) in the control group (Figure S3). As the secondary outcomes were divided by a second CUS 30 days or later, 156 of 1,438 (10.8%) allocated to IPC and 189 of 1,438 (13.1%) allocated to no IPC died within 30 days (Dennis, 2013). Overall, IPC was associated with a nonsignificant decrease in mortality among stroke patients allocated to IPC (RR = 0.83, 95% CI [0.69, 1.01]; $I^2 = 0\%$; Figure S3).

IPC-Related Adverse Events

IPC-related adverse events included influencing on normal sleep patterns (Pambianco et al., 1995), skin breaks, and risk of falls (Dennis, 2013). Two studies (Dennis, 2013; Pambianco et al., 1995) including 3,108 patients reported IPC-related adverse events, such as skin breaks, 1,555 patients were allocated to IPC group and 1,553 were allocated to the control group, respectively. The incidence of IPC-related adverse events was 2.89% (45/1,555) in the IPC group and 1.29% (20/1,553) in the control group. However, the risk of falls with injury or fractures within 30 days did not differ between the IPC and no IPC groups (RR = 1.38, 95% CI [0.82, 2.29]; Dennis, 2013). Overall, there was a significant excess of IPC-related adverse event among patients allocated to IPC (RR = 2.22, 95% CI [1.32, 3.72]; $I^2 = 0\%$; Figure S4). At the 6-month follow-up, 388 of the 1,098 (35.3%) stroke patients allocated to IPC and 396 of the 1,058 (37.4%) allocated to the control group reported swelling of the leg since the stroke (Dennis, Sandercock, Graham, Forbes, & Stroke, 2015). In addition, 24 of the 1,098 (2.2%) stroke patients allocated to IPC and 19 of the 1,058 (1.8%) allocated to the control group reported having a leg ulcer since the stroke (Dennis et al., 2015).

Disability, Living Circumstances, and Health-Related Quality of Life

The 2014 CLOTS 3 study reported outcomes of disability (Oxford Handicap Scale [OHS]; Van Swieten, Koudstaal, Visser, Schouten, & Van Gijn, 1988), living circumstances, health-related quality of life, and hospital costs based on follow-up

questionnaires returned after 6 months. The proportion of patients living in institutional care, including a nursing home or a hospital, was 25% (266/1,076) in the IPC group and 22% (233/1,039) in the routine care group. There was no significant difference in living circumstances (institutional care or not; adjusted OR = 1.11; 95% CI [0.89, 1.37]; $p = .358$).

Overall, there were no significant differences in disability with unadjusted and adjusted ORs based on the dichotomized groups (OHS 0–2 vs. 3–6). The ORs were 0.99 (95% CI [0.83, 1.19]; $p = .93$) and 0·98 (0.80–1.19; $p = .83$), respectively (Dennis et al., 2014). Regarding median health-related quality of life, the utility value for survivors had a median of 0.26 (interquartile range (IQR) –0.07 to 0.66) for IPC and 0.27 (–0.06 to 0·64), with no IPC ($p = .952$), for no IPC. Though there was a significant increase in survival by 4.5 days (148–152.5 days; 95% CI [–0.2, 9.1]) in patients allocated to IPC, IPC did not significantly improve quality-adjusted survival (IPC 27.6 days [*SD* 40.6] vs. no IPC 26.7 days [39.6]; mean difference 0.9 days, 95% CI [–2.1, 3.9]; Dennis et al., 2014).

Pulmonary Embolism

In Lacut et al. (2005) and Dai (2015), there were no PEs nor any confirmed cases of PE at postmortem (Naccarato et al., 2010). In Dennis (2013), IPC decreased the incidence of PE, as confirmed by imaging or autopsy from 2.4% (35/1,438) to 2.0% (29/1,438; OR = 0.83; 95% CI [0.50, 1.36]). There are limitations in these results because of the very small incidence of symptomatic PE in each group

Subgroup Analysis

To explore reasons for heterogeneity, we conducted subgroup analyses to investigate whether the effect of IPC therapy on calf Deep Vein Thrombosis (cDVT) prevention differed according to pathogenesis of stroke, time after stroke, and treatment modality for IPC.

Ischemic and hemorrhagic stroke. A subgroup analysis based on the type of stoke showed that IPC did not have a significant effect on DVT prevention (RR = 0.71, 95% CI [0.33, 1.54]) for ischemic stroke patients (Dennis, 2013; Pambianco et al., 1995; Wan et al., 2013), with moderate heterogeneity ($I^2 = 52\%$). IPC was associated with a significant trend in reduction of risk of DVT prevention (RR = 0.28, 95% CI [0.14, 0.56]) for hemorrhagic patients (Dai, 2015; Lacut et al., 2005; Pambianco et al., 1995; Wang, 2017) without heterogeneity ($I^2 = 16\%$; Figure S5A). Subgroup analyses stratified by type of stroke showed a strong positive effect of IPC among those with 669 hemorrhagic stroke patients in four studies (within subgroup, $p = .0003$) and no statistically significant effect among 2,492 ischemic stroke patients in three studies (within subgroup $p = .12$). Subgroup analyses testing the effect of IPC in those with ischemic stroke and hemorrhagic stroke did reveal evidence of a marginally statistically significant difference (p for subgroup difference .08). Compared with ischemic stroke patients, hemorrhagic stroke patients in the IPC group had lower risk of DVT.

Time after stroke. For DVT prevention, five studies provided separate results based on time after stroke. The pooled RR was 0.80 (95% CI [0.42, 1.54]; $I^2 = 47\%$) for three studies (Dai, 2015; Dennis, 2013; Prasad et al., 1982) involving 1,791 patients who received IPC within 72 hr of acute stroke and the RR was 0.60 (95% CI [0.22, 1.61]; $I^2 = 64\%$; Figure 5B) for three studies (Dennis, 2013; Pambianco et al., 1995; Wang, 2017) involving 975 patients who received IPC more than 72 hr after stroke. Subgroup analyses stratified by time after stroke showed that there was no significant protective effect for patients who received IPC therapy within 72 hr and more than 72 hr after stroke. An exploratory analysis testing the time when patients received IPC therapy did not show evidence of a significant interaction (p for subgroup difference .63).

Treatment modality of IPC. According to treatment modality, the method of IPC used could be divided two different ways as follows: 24 hr continuous therapy and intermittent use. Subgroup based on the type of procedure and method of IPC showed that IPC administered as 24 hr continuous use (Dennis, 2013; Lacut et al., 2005; Wang, 2017) was more effective for DVT prevention, with moderate heterogeneity ($I^2 = 50\%$) but the differences was not statistically significant (RR = 0.55; 95% CI [0.25, 1.21]). In patients who received intermittent IPC therapy, there was a nonsignificant difference in reduction in the risk of DVT (RR = 0.35; 95% CI [0.10, 1.25]; $I^2 = 72\%$; Figure S5C; Dai, 2015; Pambianco et al., 1995; Prasad et al., 1982; Wan et al., 2013; Wang 2017). Subgroup analysis comparing those that received 24 hr continuous IPC therapy versus those that received intermittent IPC use did not find differences in DVT prevention between IPC and control group (p for subgroup difference .54).

Quality Assessment

Interinvestigator agreement. The overall kappa statistic calculated for the various parameters extracted by the two investigators was 0.96 (ranged between 0.70 and 1.000), indicating an excellent degree of interinvestigator agreement.

The results of the quality assessment of the seven included trials are presented in Table S2. In general, this review revealed a relatively low overall risk of bias. Five studies were found to have a low risk of bias (Dennis, 2013; Pambianco et al., 1995; Prasad et al., 1982; Wan et al., 2013; Wang, 2017). Two out of the seven trials were found to have a high risk of bias (Dai, 2015; Lacut et al., 2005). The most common source of bias was the implementation of blinding including participants, personnel, and outcome assessment. All studies reported random sequence generation but only five studies reported how the allocation sequence was generated (CLOTS [Clots in Legs Or sTockings after Stroke] Trials Collaboration, 2014; Dai, 2015; Lacut et al., 2005; Pambianco et al., 1995; Wang, 2017). In terms of allocation concealment and

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blinding procedures, there were insufficient details in three (Prasad et al., 1982; Wan et al., 2013; Wang, 2017) and five (Dai, 2015; Pambianco et al., 1995; Prasad et al., 1982; Wan et al., 2013; Wang, 2017) of the seven trials, respectively, which may cast doubts on the nature and efficacy of the blinding process. Two studies failed to blind participants and personnel (Dennis, 2013; Lacut et al., 2005). In the follow-up on day 10, 18 patients did not have the scheduled compression duplex ultrasound (CDU) (Lacut et al., 2005). Furthermore, we believe that adequate methodology and study design is necessary to confer stronger internal validity to the results and strong association between treatment and response (El Sabbagh, Sewitch, Bezdjian, & Daniel, 2017).

Publication Bias

Publication bias was not analyzed due to the limited number of included studies.

DISCUSSION

The purpose of this meta-analysis was to assess the effectiveness and safety of IPC in preventing DVT among stroke patients by reviewing the literature. Four studies in English and three trials in Chinese that presented the effect of IPC in stroke patients on the incidence of DVT, PE, mortality, and IPC-related adverse events were reviewed. Overall, the use of IPC in stroke patients significantly reduced the risk of DVT. However, IPC improves survival but not functional outcomes, and it does not lead to a significant gain in quality-adjusted survival (Dennis et al., 2014). PEs were rare in the included RCTs of IPC methods of prophylaxis in stroke patients. The protective effect of IPC on PEs was imprecise and further investigation is needed.

Our study thoroughly searched recent literature and reviewed relevant studies. Our outcome was inconsistent with the results of a previous review of 177 patients that concluded there was insufficient evidence to support the use of IPC to reduce the risk of DVT in stroke patients (Naccarato et al., 2010). The pooled result of our study showed that IPC significantly reduced the risk of DVT in stroke patients during the scheduled treatment period. Due to the moderate heterogeneity, sensitivity analyses and subgroup analyses were performed. After exclusion of the largest study CLOTS 3 (Dennis, 2013), the magnitude and direction of the protective effect of IPC on DVT compared with that of no IPC remained unchanged.

The pooled result showed that IPC was associated with a nonsignificant decrease in mortality. Due to the small number of included trials and the low incidence rate of events, this conclusion may not be reliable.

The secondary outcome of CLOTS 2014 showed that IPC was associated with a significant increase in survival at the 6-month follow-up. In contrast, IPC was not associated with significant improvement in disability, proportions of patients living at home, quality of life, or quality-adjusted survival (Dennis et al., 2014). Results from CLOT 3 showed that the proportion of patients surviving with an OHS of 5 significantly increased, meaning that they were in bed or were chair-bound and required complete care. This result indicated that most of the deaths that may result from PE and might be prevented by IPC occurred in patients with severe strokes who would be expected to have poor functional outcomes (Dennis et al., 2014). Therefore, patients who survive because IPC effectively reduces the risk of DVT would be expected to have poor functional status that is unacceptable to them or their families. For this reason, IPC was not associated with quality-adjusted survival. The results raise clinical and ethical questions for clinicians in making decisions to give prophylaxis for DVT to patients after stroke.

Two studies reported IPC-related adverse events, including disturbance in sleep patterns, skin breaks, lower limb ischemia, and amputation or falls with injury. The pooled result showed that patients allocated to IPC had more skin breaks compared with those allocated to no IPC but there were no significant differences in the risk of falls with injury or fractures within 30 days. In the 6-month follow-up of CLOTS 3, 44 patients in the IPC group and 20 in the no IPC group had skin breaks. However, few of the skin breaks or falls with injury were attributed to IPC by local researchers.

Because patients with IPC in situ typically lie on their back with their heels pressing into the mattress, it is expected that there may be sheering injury on their back if strategies to prevent it are not put in place. Most adverse events occurred when IPC had been removed, or skin breaks affected the heels (which are not covered by the IPC sleeves) and thus were unlikely to be due to the IPC (Dennis, 2013). Due to the lack of blinding of the nursing staff, these adverse event data are therefore prone to ascertainment bias (Dennis et al., 2015). The authors of CLOTS 3 attempted to detect post-phlebitic leg syndrome including leg swelling and ulcers at the 6-month follow-up. In the 6-month follow-up, it is not clear whether these symptoms indicate the development of post-phlebitis leg syndrome, or if they simply reflect comorbidities such as heart failure or ulcers due to other causes (Dennis et al., 2015). These questions were unlikely to be specific due to the high frequency of swelling in stroke affected limbs and leg ulcers of other types.

A systematic review and meta-analysis by Craigie et al. (Craigie et al., 2015) investigated adherence to mechanical thromboprophylaxis, and 75% adherence was found. In clinical practice, clinicians should consider the issue of adherence when adopting IPC as mechanical prophylaxis.

The CLOTS 3 did a within-trial cost-utility analysis to assess the cost-effectiveness of IPC in stroke patients. The incremental cost-effectiveness ratio showed that IPC might be used if a decision maker is willing to pay more than £610.88 for an additional day of quality-adjusted survival (Dennis et al., 2015).

Study Limitations

There were several limitations of the review that impacted the generalization of its findings. First, a major limitation of our

study was the small number of trials that made the sample less representative of the population and decreased the robustness of the results.

Second, there was moderate heterogeneity in the DVT prevention outcome comparing IPC with no IPC. Although we included studies that were RCTs, some studies' methodological quality was low, which may have contributed to the heterogeneity in the pooled estimates. Additional sources of heterogeneity included the different clinical settings, the baseline characteristics of patients, the definitions of DVT, the methods of event ascertainment, type of stroke, treatment modality of IPC, and degree of adjustment for potential confounders (Polachek, Touma, Anderson, & Eder, 2017). Due to the statistically significant heterogeneity in the pooled results, we used random-effects model to include an estimate of variability. Sources of variability were partially explored by performing subgroup analyses. According to the results of subgroup analyses, heterogeneity was not related to whether the trials used either 24 hr continuous IPC therapy or intermittent IPC therapy, or whether IPC was provided within 72 hr after stroke or there was a delay in IPC therapy. By contrast, when analyses were restricted to hemorrhagic patients (based on only four studies [Dai, 2015; Lacut et al., 2005; Wan et al., 2013; Wang, 2017]), the heterogeneity between trials was low ($p = .31$; $I^2 = 16\%$). In three trials that compared IPC with no IPC alone (there was not any type of therapy measure in the control group including pharmacological, ES, or rehabilitation intervention), IPC significantly reduced the risk of DVT without heterogeneity. Therefore, the therapy measure in the control group may be one reason for the resulting heterogeneity in the pooled estimates. Baseline pathogenesis of the stroke may be a reason for heterogeneity in pooled results. However, it was impossible to assess the effect of factors including age, the severity of the stroke, and any underlying disease that may have produced a high risk for DVT due to the limited information available.

Finally, the quality of included studies was moderate. The method of randomization generation was unclear in studies by Wan et al. (2013) and Prasad et al. (1982). Blinding of outcome data was unclear in five studies (Dai, 2015; Pambianco et al., 1995; Prasad et al., 1982; Wan et al., 2013; Wang, 2017).

CONCLUSIONS

There is clear evidence of the effect of IPC in reducing the risk of DVT and improving of survival over 6 months of follow-up for both ischemic and hemorrhagic stroke patients. However, IPC does not significantly improve quality-adjusted survival. Clinicians should take functional status and quality of life into consideration when making decisions for stroke patients. There is a need to develop guidelines for mechanical thromboprophylaxis applications and safe use, and to implement educational programs for healthcare providers to improve performance, enhance patient' outcomes, and achieve effectiveness of mechanical prophylaxis devices. **WVN**

LINKING EVIDENCE TO ACTION

- Intermittent pneumatic compression could be a strategy to prevent DVT in stroke patients without significant adverse events attributed to IPC, and should be applied to stroke patients in institutional settings.
- Intermittent pneumatic compression, whether used continuously 24 hr a day or as intermittent therapy, there is no significant difference according to the pooled result in DVT prevention.
- Clinicians and nurses should pay attention to IPC-related events, such as skin breaks and risk of falls.
- Research is necessary to determine whether intermittent pneumatic compression could reduce the incidence of mortality or PE.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site:

Figure S1. Flow chart of the systematic literature search.
Figure S2. Forest plot showing the effect of intermittent pneumatic compression (IPC) on the risk of deep venous thrombosis (DVT) compared with no IPC. Studies are listed according to the order of their year of publication. CI, confidence interval; RR, risk ratio.
Figure S3. Forest plot showing the effect of intermittent pneumatic compression (IPC) on the risk of mortality compared with no IPC. Studies are listed according to the order of their year of publication. CI, confidence interval; RR, risk ratio.
Figure S4. Forest plot showing the effect of intermittent pneumatic compression (IPC) related events compared with no IPC. Studies are listed according to the order of their year of publication. CI, confidence interval; RR, risk ratio.
Figure S5A. Forest plot of ischemic and hemorrhagic subgroup analysis showing the effect of intermittent pneumatic compression (IPC) on the risk of deep venous thrombosis (DVT) compared with no IPC. Studies are listed according to the order of their year of publication. CI, confidence interval; RR, risk ratio.
Figure S5B. Forest plot of within 72 hr or more than 72 hr subgroup analysis showing the effect of intermittent pneumatic compression (IPC) on the risk of deep venous thrombosis (DVT) compared with no IPC. Studies are listed according to the order of their year of publication. CI, confidence interval; RR, risk ratio.
Figure S5C. Forest plot of continuously or intermittent subgroup analysis showing the effect of intermittent pneumatic compression (IPC) on the risk of deep venous thrombosis (DVT) compared with no IPC. Studies are listed according to the order of their year of publication. CI, confidence interval; RR, risk ratio.
Figure S6. Cochrane risk of bias tool for randomized controlled trials. Green (+)—low risk of bias; yellow (?)—unclear from the study; red (–)—high risk of bias.
Table S1A. Characteristics of Included Studies.
Table S1B. Characteristics of Included Studies.
Table S2. Assessment of Bias.

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