Knee-length graduated compression stockings for thromboprophylaxis in air travellers: A meta-analysis

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OBJECTIVE: To systematically review the randomized controlled trials that have evaluated the efficacy of knee-length (KL) compression stockings for thromboprophylaxis in air travellers.

METHOD: After an electronic database search, the randomized controlled trials that studied passengers on long-haul flights were selected and analyzed to generate summative data.

RESULTS: Nine trials studying participants using KL stockings were analyzed. Forty-six of 1261 participants randomly assigned to the control group developed deep vein thrombosis (DVT), compared with two of 1237 participants (0.16%) in the KL stockings group.

Graduated compression stockings (GCS) are an effective and commonly used means of mechanical thromboprophylaxis (1-3) in both the hospitalized and air-travelling populations. John Homans (4), a Boston surgeon, made the first report of two patients with deep vein thrombosis (DVT) following prolonged air travel. In 1977, Symington and Stack (5) introduced the term 'economy class syndrome' when they reported DVT that occurred in eight patients shortly after flying economy class. It is evident now that traveller's thrombosis is present in all classes (economy, business or any other class), and all groups are at equal risk of developing symptomatic or asymptomatic DVT, and pulmonary embolism. In the past decade, more than 200 cases of traveller's DVT have been reported in the international literature (6).

However, despite the early recognition of an association between longer air travel and DVT, it was not until recently that more informative studies have been performed. The risk for venous thromboembolism after long-haul flights is a controversial issue. Three case control studies estimate the RR of DVT development after long-haul flights to range from 1.0 (95% CI 0.3 to 3.0) to 3.98 (95% CI 1.9 to 8.4) (7). The published data, drawn from case reports, retrospective analysis, case control studies or randomized controlled trials, have been criticized because of inadequate design or sample size. The present meta-analysis and future studies are important because the impact on public health is significant. Given that the number of both air and land passengers is predicted to rise (it was estimated at more than two billion in 2006), it is vital that the information given to travellers of their thrombosis risk and of preventive strategies is evidence-based and thorough. Accordingly, by systematic review of the literature, we

The weighted risk difference was -0.034, which indicated that the absolute difference was 3.4% in the incidence of DVT, in favour of KL stockings. The number needed to treat with KL stockings to avoid one case of DVT was 29.4. However, there was significant heterogeneity among trials. The RR for DVT was 0.08 in high-risk participants and 0.14 in low- to medium-risk participants.

CONCLUSION: KL stockings are effective for thromboprophylaxis in air travellers at low, medium and high risk of DVT. The use of KL stockings should form an important part of air traveller education on lowering the burden of DVT. The results of the present meta-analysis can be used to advise travellers on their risk of DVT and preventive strategies.

Key Words: Air travellers; Compression stockings; DVT; Long-haul flight; Thromboprophylaxis

attempted to establish the effectiveness of knee-length (KL) elastic stockings for thromboprophylaxis in subjects travelling by air for at least 4 h to 8 h.

METHODS

Relevant studies published between January 1976 and June 2006 were identified through the MEDLINE, EMBASE, CINAHL and Cochrane Library databases. The terms "stocking/s", "sock/s" and "hosiery/hosieries" were used in combination with the medical subject headings "thromboprophylaxis", "knee length graduated compression stockings", "thromboembolism in air travel" and "travelers' thrombosis". Relevant articles referenced in these databases were obtained. Each article was then critically reviewed to assess eligibility for inclusion in the present meta-analysis (Table 1). Study cohort size was not a criterion for inclusion. Randomized controlled trials of KL compression stockings among airline passengers were selected. Stockings used in long-haul flights were class I and II GCS (ankle pressure 14 mmHg to 30 mmHg). Use of other forms of thromboprophylaxis such as low molecular weight heparin (LMWH) and acetylsalicylic acid (ASA) among the studied group of subjects was mentioned in a few reviewed trials. However, the exact type, dose, and their effect was not mentioned or studied. Comparisons of DVT incidence were made between air passengers assigned to KL stockings or the control group (no stockings) and an analysis was performed. ORs were calculated and a fixed effect model was applied with tests for heterogeneity. Where heterogeneity was detected, a random effects model was also applied. In addition, a meta-regression analysis was performed to assess the relative benefit of KL stockings on airline passengers. In the sensitivity analysis,

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TABLE 1
Trial inclusion criteria

Randomized, controlled, prospective clinical trial that studied the use of knee-length elastic stockings for thromboprophylaxis in air travellers

Use of objective diagnostic tests for determination of DVT, eg, venous duplex ultrasonography

Studies that had an end point of DVT

Use of blinded interpretation of diagnostic tests. Each positive diagnostic test was evaluated by two different radiologists unaware of the reported conclusion of the other

Use of predefined criteria for abnormal test results. A positive duplex scan was defined as when thrombus was seen and/or the vein was not compressible

Study cohort sample of any size

Knee-length stockings (class I, II and/or ankle pressure of 14 mmHg to 30 mmHg)

DVT Deep vein thrombosis

Figure 1) Statistical analysis of selected trials

0.5 was added to each cell frequency for trials in which no event occurred in either the treatment or control group, according to the method recommended by Deeks et al (8). The analysis was carried out using Stata software (Version 9; Stata Corp, USA) running on a personal computer. Outcomes were calculated using both fixed effect and random effect models. When neither approach fit well, the fixed effect model was used (8). The term 'high-risk' applies to passengers with a history of thromboembolism, occult or overt malignancy, or a coexisting procoagulant condition. The 'medium-risk' population included passengers with superficial or deep venous insufficiency, disabilities that limit mobilization and recent major pelvic surgery. The 'low-risk' population among air passengers included age older than 50 years, immobilization, poor fluid intake, and sitting in crowded and cramped conditions for at least 8 h to 12 h (Table 2).

RESULTS

Nine clinical studies (9-14) were retrieved from the literature (Table 3). The characteristics of the included trials are given in Table 4. The analysis of methodological qualities of the included studies is given in Table 5. Each arm of trials 11 to 13

TABLE 2
Deep vein thrombosis (DVT) risk factors in air travellers

Flight-related risk factors

Immobilization (sitting in a narrow space for at least 8 h)

Dehydration (poor fluid intake, dry environment, drinking)

Cramped conditions (narrow and crowded seating)

Hypoxia (pre-existing respiratory disorders, normobaric or hypobaric hypoxia)

Passenger-related risk factors

Hypercoagulability of any origin

Elderly people

Obesity, use of contraceptive pills and hormone replacement therapy

History of DVT or pulmonary embolism

Malignant conditions

Recent pelvic or hip surgery

Varicose veins

was analyzed as a separate randomized controlled trial. In three trials, no events were observed in the KL stockings or in the control groups and, thus, their contribution was negligible in the calculation of pooled ORs and risk ratios. The remaining six randomized controlled trials were analyzed. All DVTs seen in travellers were found to be asymptomatic and infrapopliteal. There was no description of long-term follow-up of these patients with asymptomatic DVT in any trial. Furthermore, there was no separate evaluation of fatal or nonfatal pulmonary embolism in any randomized controlled trial. Forty-six of 1261 (3.64%) participants randomly assigned to the control group developed DVT, compared with two of 1237 (0.16%) participants in the KL stockings group. Among these participants, the weighted risk difference (Figure 1) was -0.034 (95% CI -0.045 to -0.023; $P < 0.001$). This demonstrates that the absolute difference in the incidence of DVT in favour of KL stockings was 3.4% (95% CI 2.3% to 4.5%; $P < 0.001$). Therefore, the number needed to treat with KL stockings to avoid one case of asymptomatic DVT is 29.4. However, there was significant heterogeneity among the trials ($\chi^2_8 = 32.5$; $P < 0.001$). Scurr et al (9) showed very significant heterogeneity, while five trials (four by Belcaro et al and one by Cesarone et al) showed moderate heterogeneity. Three trials by Cesarone et al did not contribute to the calculation of heterogeneity. All subjects in both the randomized and control groups were effectively screened for DVT before the flights. There was no record available suggesting that a single technologist performed pre and postflight venous duplex scans. Furthermore, one postflight evaluating technologist was not blinded to the history of the examinees, which possibly introduced bias in favour of DVT diagnosis in the high-risk group. The weighted OR was 0.45 (95% CI 0.30 to 0.68; $P < 0.001$), indicating a 55% odds reduction. The incidence of DVT observed when subjects were wearing stockings was 18.8 times lower than in controls.

The RR of DVT in high-risk participants was 0.08 (95% CI 0.02 to 0.34, $\chi^2 = 0.60$, $df = 1$, $z = 3.42$; $P < 0.0006$) and was 0.14 for low- and medium-risk participants (95% CI 0.03 to 0.79, $\chi^2 = 0.08$, $df = 2$, $z = 2.23$; $P < 0.03$), indicating a more thromboprophylactic effect of GCS in the high-risk population than the low- and medium-risk populations. Furthermore, meta-analysis

TABLE 3
Trials used in meta-analysis

Trial	Diagnostic test	Stocking group (% DVT)	Control (% DVT)
Scurr et al (9) 2001	Venous duplex	0/100 (0)	12/116 (10)
Belcaro et al (10) 2001, LONFLIT 2	Venous duplex	1/411 (0.2)	19/422 (4.5)
Belcaro et al (11) 2002, LONFLIT 4-1a	Venous duplex	0/179 (0)	4/179 (2.2)
Belcaro et al (12) 2002, LONFLIT 4-1b	Venous duplex	0/136 (0)	3/135 (2.2)
Cesarone et al (13) 2003, LONFLIT 4-3b	Venous duplex	0/64 (0)	2/66 (3.0)
Belcaro et al (14) 2003, LONFLIT 5	Venous duplex	1/103 (1.0)	6/102 (5.9)
Cesarone et al (12) 2003, LONFLIT 4-2a	Venous duplex	0/97 (0)	0/98 (0)
Cesarone et al (13) 2003, LONFLIT 4-2b	Venous duplex	0/75 (0)	0/71 (0)
Cesarone et al (13) 2003, LONFLIT 4-3a	Venous duplex	0/72 (0)	0/72 (0)

DVT Deep vein thrombosis

TABLE 4
Characteristics of trials used in the analysis

Trial	Flight duration	Type of passengers	Confounding variables
Scurr et al (9) 2001	≥8 h	All passengers	Stockings with ankle pressure of 20–30 mmHg
Belcaro et al (10) 2001, LONFLIT 2	≥12 h	High-risk	Stockings with ankle pressure of 25 mmHg
Belcaro et al (11) 2002, LONFLIT 4-1a	4–8 h	Low- and medium-risk	Stockings with ankle pressure of 14–17 mmHg
Belcaro et al (12) 2002, LONFLIT 4-1b	4–8 h	Low- and medium-risk	Stockings with ankle pressure of 12–18 mmHg
Cesarone et al (13) 2003, LONFLIT 4-2a	4–8 h	Low- and medium-risk	Stockings with ankle pressure of 12–18 mmHg. DVT and ankle edema were assessed
Cesarone et al (12) 2003, LONFLIT 4-2b	4–8 h	Low- and medium-risk	Stockings with ankle pressure of 12–18 mmHg. DVT and ankle edema were assessed
Cesarone et al (13) 2003, LONFLIT 4-3a	4–8 h	Low- and medium-risk	Stockings with ankle pressure of 12–18 mmHg, ASA and LMWH
Cesarone et al (13) 2003, LONFLIT 4-3b	4–8 h	Low- and medium-risk	Stockings with ankle pressure of 12–18 mmHg, ASA and LMWH
Belcaro et al (14) 2003, LONFLIT 5	Not stated	High-risk	Stockings with ankle pressure of 14–17 mmHg

ASA Acetylsalicylic acid; DVT Deep vein thrombosis; LMWH Low molecular weight heparin

TABLE 5
Methodological quality of included trials

Trial	Study design	Inclusive criteria	Exclusive criteria	Sample size calculation	Baseline comparable	Blinding	Intention-to-treat analysis
Scurr et al (9) 2001	RCT	Given	Given	Not stated	Stated	No	Done
Belcaro et al (10) 2001, LONFLIT 2	RCT	Given	Not given	Not stated	Not stated	No	No
Belcaro et al (11) 2002, LONFLIT 4-1a	RCT	Not given	Given	Not stated	Stated	No	Done
Belcaro et al (12) 2002, LONFLIT 4-1b	RCT	Not given	Given	Not stated	Stated	No	Done
Cesarone et al (12) 2003, LONFLIT 4-2a	RCT	Not given	Given	Not stated	Stated	No	No
Cesarone et al (12) 2003, LONFLIT 4-2b	RCT	Not given	Given	Not stated	Stated	No	No
Cesarone et al (13) 2003, LONFLIT 4-3a	RCT	Not given	Given	Not stated	Stated	No	Done
Cesarone et al (13) 2003, LONFLIT 4-3b	RCT	Not given	Given	Not stated	Stated	No	Done
Belcaro et al (14) 2003, LONFLIT 5	RCT	Given	Given	Not stated	Stated	No	Done

RCT Randomized controlled trial

showed that GCS were more effective than no GCS in preventing DVT in trials that studied high-risk subjects (10,14).

Two of the 514 participants (0.38%) developed DVT in the GCS group, while 25 of the 524 subjects (4.7%) in the control group (no GCS) developed asymptomatic DVT.

DISCUSSION

The results of the present meta-analysis indicated that KL GCS are a valuable means of thromboprophylaxis in air travellers.

However, there was significant heterogeneity among the trials. The first possible cause of heterogeneity may be that the researcher assessing the DVT was not blind to group allocation. The second possible cause of heterogeneity was the presence of confounding variables among subjects testing the efficacy of the elastic stockings, eg, exercise, standing, stretching, drinking adequate water – such factors are likely to affect DVT development. Also, ‘avoiding constrictive clothes’ was suggested as another thromboprophylactic method in both

the treatment and control groups. The results of trials included in the present meta-analysis were not consistent. There were no symptomatic DVTs and the incidence of asymptomatic DVT reported in the control group was varied and wide-ranging – from 0% to 10% in the control group and from 0% to 1% in the KL stocking group. Patient bias (frequent mobilization of subjects in the KL stocking group or subjects drinking more liquids) may be responsible for some changes in the final outcome, but it was not clearly quantified in the trials. In addition, a single research group conducted most of these trials, with subjects from the Western hemisphere only.

The LONFLIT trials (9-14) provide invaluable evidence of the risk of DVT in the air travellers. The thrombosis risk is greater following a journey of more than 8 h. Those at greater risk are travellers with a history of venous thromboembolism. Based on the best evidence available, the risk of symptomatic DVT after flights of more than 12 h is 0.5% (15). The quantitative risk of lower limb DVT following long-haul flights in high-risk subjects is 5% per flight. For lower risk subjects, the risk is 1.6% per flight (16). Interestingly, all DVTs in the passengers included in these trials were asymptomatic, but due to lack of long-term follow-up data, it is difficult to know the exact nature of any clinical sequelae after the conclusion of the trials. Asymptomatic DVT in clinical settings has been found to be responsible for post-thrombotic syndrome and other sequelae (17) of venous thrombosis. Therefore, asymptomatic DVT in air travellers should not be ignored.

Routine DVT prevention protocols for travel thrombosis remain controversial. KL compression stockings have been used in many trials and are effective. Class I and II KL GCS with ankle pressures of between 14 mmHg and 30 mmHg have shown a reduction in lower limb DVT in air travellers (16). A few trials recommend regular exercise (5 min to 10 min per hour), not leaving baggage between seats and regularly drinking water (100 mL to 150 mL per hour) to further reduce DVT risk. In a trial of 400 mg ASA for three days versus a single 1 mg/kg dose of LMWH (Clexane; sanofi-aventis, France), ASA was found to be ineffective, but LMWH appeared to reduce the incidence of traveller DVT (18). In summary, in both high-risk and low-risk air passengers, KL GCS appear to be effective in reducing the risk of DVT. However, there is currently insufficient evidence to recommend routine pharmacological intervention for thromboprophylaxis in air travellers. In addition, there are still questions about whether hypobaric hypoxia is a true risk for DVT. Findings by Toff et al (19) do not support the hypothesis that hypobaric hypoxia – to the

degree that may be encountered during long-haul air travel – is associated with prothrombotic alterations in the hemostatic system in healthy individuals at low risk of venous thromboembolism. The findings of the epidemiological studies indicate that the risk of venous thrombosis increases by approximately threefold after a long-haul flight. This increased risk applies to other forms of travel, such as car, bus or train, where travellers are exposed to prolonged seated immobility. The risk increases with the duration of travel and with multiple flights within a short period (19). Medical practitioners and the travelling public need to be aware that it appears to be seated immobility that is the major risk factor, including travelling by any means of transport, watching a Wagner opera or sitting at a computer all day. No study has identified any risk factor specific to the flight environment. However, our meta-analysis supports the conclusions made by previous reviews (20,21). Based on the available evidence, KL stockings may be recommended for thromboprophylaxis in air travellers, especially in high-risk passengers.

IMPLICATIONS

Doctors are increasingly being asked to advise on the risk of travel-related DVT, as well as the need for and nature of appropriate thromboprophylaxis. The present meta-analysis can suggest advice, but further research is required before GCS can be standard prophylaxis for flight-related thromboses. Given the low incidence of DVT, studies with global representation and a greater number of subjects should be conducted. In addition, the optimal compression pressure of stockings for airline passenger thromboprophylaxis requires further study. DVT risk stratification should also be considered before recommending stockings in any given scenario. Because there is significant heterogeneity among the trials, possible sample contamination from subject bias and the fact that all diagnosed DVT among air travellers was asymptomatic and infrapopliteal, the present review cannot justify recommending KL stockings for every passenger on long-haul flights. However, air travellers with a high risk of DVT may be considered for thromboprophylaxis with KL stockings until a major multicentre randomized controlled trial explores the role of compression stockings in air travellers.

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