

Venous Thrombosis from Air Travel: The LONFLIT3 Study

Prevention with Aspirin vs Low-Molecular- Weight Heparin (LMWH) in High-Risk Subjects: A Randomized Trial

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The LONFLIT1 and 2 studies established that in high-risk subjects after long (>10 hours) flights, the incidence of deep venous thrombosis (DVT) may be between 4% and 6%. The LONFLIT3 study aimed to evaluate methods of prevention in high-risk subjects. Of 467 subjects contacted for the study, 300 were included. These 300 subjects at high risk for DVT were randomized, after informed consent, into three groups: 1) a control group that had no prophylaxis; 2) an aspirin treatment group, in which patients were treated with 400 mg (tablets of oral, soluble aspirin; one dose daily for 3 days, starting 12 hours before the beginning of the flight); and 3) a low-molecular-weight heparin (LMWH) group, in which one dose of enoxaparine was injected between 2 and 4 hours before the flight. The dose was weight-adjusted (1000 IU [equivalent to 0.1 mL] per 10 kg of body weight). Subjects with potential problems due to prophylaxis with aspirin or LMWH or at risk of drug interactions were excluded. Of the 100 included subjects in each group, a total of 249 subjects completed the study (dropouts due to low compliance or traveling/connections problems were 17%). Age and sex distribution were comparable in the three groups as well as risk distributions. Mean age was 47 (range, 28–75; SD, 11; 65% males). Of the 82 subjects in the control group, there were 4.82% of subjects with DVT with two superficial thromboses. In total 4.8% of limbs suffered a thrombotic event. Of 84 subjects in the aspirin treatment group, there were 3.6% of patients with DVT and three superficial thrombosis. In total 3.6% of limbs had a thrombotic event. In the LMWH group (82 subjects), there were no cases of DVT. One superficial thrombosis was documented. In total only 0.6% of limbs had a thrombotic event ($p < 0.002$ in comparison with the other two groups). DVT was asymptomatic in 60% of subjects; 85% of

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DVTs were observed in passengers in non-aisle seats. Mild gastrointestinal symptoms were reported in 13% of patients taking aspirin. One dose of LMWH is an important option to consider in high-risk subjects during long-haul flights.

Introduction

Recently, scientific and media attention has been generated concerning the risk of venous thrombosis and embolism after long-haul flights.¹ Attention was generated by the death of a 27-year-old woman from pulmonary embolism after a flight from Australia to the United Kingdom.² However, there is still limited evidence for causality¹ because no prospective evaluation has been performed to link long-distance flights to venous thrombosis. Homans first reported venous thrombosis after air travel in the 1950s, presenting the case of a doctor in whom deep venous thrombosis (DVT) developed after a 14-hour flight.³ The condition was termed *economy class syndrome*.⁴ Venous stasis, possibly caused by prolonged sitting in a limited space was considered to be an important causal factor. Similar circumstances such as sitting for hours in shelters in London during World War II had been shown to be associated with up to a sixfold increase in sudden death from pulmonary embolism.⁵

Prolonged travel has also been reported to be associated with DVT and pulmonary embolism.⁶ In a recent case-control study including 788 patients, no increased risk of DVT among travelers was found and only 17 had a history of air travel.⁸ However, another case-control study reported that a history of recent travel was found almost four times more often in patients with DVT than in control subjects.⁶ Compression of veins such as the popliteal vein on the edge of the seat could be a contributing factor to venous stasis and DVT. Hemoconcentration, due to decreased fluid intake and water loss in the dry atmosphere of airplane cabins, has been implicated⁷ together with the diuretic effect of alcohol. Another study reported that a history of recent travel was found almost four times more often in patients with DVT than in controls.⁶ In another study, the coroner for the area including Heathrow airport in London reported 61 deaths in arriving passengers over 3 years, 11 due to pulmonary embolism. In the same period, venous thromboembolism was attributable to only one of 28 deaths in passengers waiting to embark.⁹ Biochemical changes have

been reported in healthy volunteers during simulated long flights.¹⁰ Plasma viscosity, packed cell volume, albumin concentrations, fluid balance, and lower limb size were measured. No dehydration was shown, but there was retention of fluid corresponding to an approximate 1 kg increase in body weight. This study, however, did not consider the changes in cabin-related factors such as decreased air pressure, mild hypoxia, and low humidity,¹¹ which are difficult to reproduce in laboratory conditions. These factors clearly distinguish the effects of long-haul air travel from other types of travel. The decreased air pressure and relative hypoxia may reduce fibrinolytic activity and cause release of vein wall factors that lead to venous stasis.¹² The hypobaric environment may increase activated coagulation.¹³ Further prospective epidemiologic studies are required to identify the incidence of this condition and to define subjects at higher risk. The ideal prospective study should screen many passengers before and after prolonged flights.

Current evidence suggests that any association between symptomatic DVT and long-distance flights is weak and that its incidence is probably lower than the impression given by recent publicity. However, the prevalence of DVT may be particularly high in high-risk subjects. Many airlines claim that thromboembolism usually develops after the flight when the passenger had left the airplane or that a thrombus might have been present at the beginning of the flight so that they are not involved with the problem. In the past no advice has been given to passengers, but based on recent evidence^{14,17} airlines have now started to give advice¹⁸ suggesting methods to avoid *stasis and circulatory problems*, without mentioning thrombosis. From experience with prophylaxis, appropriate measures to prevent DVT might include general advice to passengers to stand up, and stretch, exercise, drink water, avoid putting baggage under the seat to have more leg space and avoid constrictive clothes. Subjects with risk factors for DVT such as a history of DVT, hormonal treatment, malignancy, or recent surgery should carefully discuss additional protective measures with their doctors, including postpon-

ing the flight. Further preventive measures might include elastic stockings, and antithrombotic prophylaxis with a low-molecular-weight heparin. There is no evidence that antiplatelet agents may be effective in this condition.

The aim of this study was to evaluate the protective effects of low-molecular-weight heparin versus aspirin for DVT prevention in high-risk subjects in long-haul flights.

The LONFLIT1 and LONFLIT2 Studies

In the LONFLIT1 study, the aim was to evaluate the incidence of DVT in low-risk subjects after long-haul flights. There were 355 low-risk subjects completing the study. Subjects had low risk for DVT (mean age 46 years; SD, 11). A second group of 389 high-risk subjects was also studied (mean age 46.4 years; SD, 12). There were no differences between the two groups. The definition of higher risk for DVT was based on a previous episode of DVT, coagulation disorders, severe obesity or limitation of mobility due to bone or joint problems, neoplastic disease within the previous 2 years, or large varicose veins.^{18,19} The average flight duration was of 12.4 hours (range, 10–15 hours). B-mode and power ultrasound were used to evaluate DVT before and after the flights. The femoral and popliteal veins were examined with compression ultrasound after the flights.^{18,19} In the low-risk group, there were no DVTs. In the high-risk group, 11 patients (2.7%) had 13 DVT (in two subjects, there was a femoral DVT at one side and a popliteal DVT at the opposite side). Therefore, there were 13 DVTs in 778 limbs (1.6%). Four DVTs (1.02%) were proximal (femoral vein) and seven were distal (0.77%; popliteal or tibial veins). There were 19 thrombotic events (13 DVTs and six superficial thromboses). In total there was a thrombotic event in 4.8% of subjects and in 2.4% of limbs; 18 of 19 thromboses (94.7%) were observed in subjects sitting in window or central seats.

The LONFLIT2 study was a prospective, randomized evaluation of DVT prevention with below-knee elastic stockings. The aim was to evaluate the incidence of DVT in high-risk subjects randomized into an elastic compression and a control group. The 833 (90.2% of 922 included) subjects who completed the study were selected according to the same flight criteria used in the

previous study. Subjects were at high risk for venous thrombosis (the definition of high-risk was equivalent to the LONFLIT1 study). Mean age was 44.8 years (SD, 9). The average flight duration was 12.53 hours (range, 10–15 hours). Ultrasound scanning (Sonosite) was made before flights (within 48 hours before) and within 24 hours after. Commercially available, below-knee, graduated compression stockings with maximum compression at the ankle of 25 mm Hg were used. Stockings were put on between 6 and 10 hours before the study flight. In the 422 subjects in the control group, we detected 22 DVTs in 19 subjects (4.5%); in three subjects, DVT was present in both limbs. There were eight superficial thromboses. The incidence of DVT was 2.6% considering all limbs. Among the 411 subjects with stockings, the DVT incidence was significantly decreased (one DVT equivalent to 0.24% of subjects and 0.12% of limbs; $p > 0.02$). DVTs were observed in subjects sitting in window or central (non-aisle) seats. Therefore, stockings decrease the incidence of DVT by 18.75 times in long-haul flights in high-risk subjects.

Patients and Methods: The LONFLIT3 Study

In this part of the study, 467 subjects at high risk for DVT were contacted; 167 subjects were excluded for several non-medical, travel-related problems or inconvenient evaluation time; the remaining 300 were randomized into three groups to evaluate two types of prophylaxis in long-haul flights:

1. Control group: no prophylaxis.
2. Aspirin treatment group: subjects were treated with 400 mg (tablets of oral, soluble aspirin; one dose daily for 3 days, starting 12 hours before the beginning or the flight).
3. Low-molecular-weight heparin (LMWH) group: one dose of enoxaparin (Clexane, Rhone-Poulenc-Rorer, AVENTIS) was injected between 2 and 4 hours before the flight; the dose was weight adjusted, 1000 IU (equivalent to 0.1 mL) per 10 kg of body weight (i.e., for a 60-kg subject, a dose of 6000 IU was used; for an 80-kg subject, a dose of 8000 IU was used). High-risk criteria for DVT are those previously indicated in LONFLIT studies 1 and 2^{18,19}; pre-

vious episode of DVT, coagulation disorders, severe obesity or limitation of mobility due to bone or joint problems, neoplastic disease within the previous 2 years, or large varicose veins.

In the scanning protocol (before-after flights), Sonosite scanners with a 7.5- to 10-MHz probe (Sonosite, Bothell, Washington) were used evaluating the venous system by compressing the major veins (femoral, popliteal).

Exclusion criteria were cardiovascular diseases or any clinically relevant disease requiring medical treatment, bone or joint problems and problems limiting mobility, diabetes mellitus, hypertension, severe obesity, and recent thrombosis or the presence of thrombi at the pre-flight examination.

Suggestions to passengers (i.e., mild exercise, walking, drinking water and avoiding salty food, avoiding baggage restricting leg motion) were given. Subjects with potential problems due to prophylaxis with aspirin or LMWH or at risk of drug interactions were excluded. Compression stockings were not used in this study because the results from the LONFLIT1 and 2 studies were not available.

Statistical analysis was conducted using non-parametric tests and the analysis of variance considering the event-free subjects completing the protocol and calculating the incidence of events (DVT, superficial thrombosis) considering individuals and limbs.

Results

Of the 100 included subjects in each group, a total of 249 subjects completed the study (Table I). Dropouts were due to low compliance or traveling and connection problems (17 in the control group, 16 in the aspirin group, and 18 in the LMWH group). Age and sex distribution were comparable in the three groups as were risk factor distributions. The overall mean age was 47 years (range, 28–75 years; SD, 11; 65% males).

In the control group, of 82 subjects (mean age, 46 years; SD, 11; M:F, 50:32), four (4.82%) subjects had a DVT (equivalent to 3.6% of limbs). There were also two superficial thromboses. In total, 4.82% limbs had a thrombotic event.

In the aspirin-treated group, of 84 subjects (mean age, 48 years; SD, 10; M:F, 51:33), three

subjects (3.6%) had DVT (1.8% of limbs); there were two superficial thromboses. In total 3.6% of limbs had a thrombotic event.

In the LMWH-treated group, in the 82 subjects (mean age, 47 years; SD, 12; M:F, 48:34), no DVT was observed. One superficial thrombosis was documented. In total only 0.6% of limbs had a thrombotic event ($p < 0.002$ in comparison with the other two groups).

In this study, 85% of DVTs (in the three groups) were observed in passengers in non-aisle seats. Mild side effects due to aspirin treatment were observed (gastrointestinal symptoms that disappeared when treatment was discontinued) in 13% of patients taking aspirin. No side effects were observed with LMWH. Approximately 60% of the thrombotic events were completely asymptomatic. No difference was observed in the distribution of thrombotic events between men and women. Of the seven females who had a thrombotic event, three were taking oral contraceptives.

Conclusions

Media reports have discussed flight thromboembolism and had the merit of increasing attention on a preventable disease.²⁰ British Airways now specifically mentions in the *High Life* magazine that exercise prevents circulatory problems and helps "...your blood from becoming sluggish, something which can happen if you sit..."²² Also detailed verbal advice is given during flights. Airlines are under more pressure to provide medical care in flights. Emergencies in planes²² are more and more frequent. However, the percentage of recorded medical episodes in flight are: fainting, 22%; cardiac events, 12%; gastrointestinal problems, 12%; seizure or stroke, 11%; respiratory problems, 11%. Limited data are available concerning DVT or pulmonary embolism which occur, if detected, mostly in the hours after the flight. It is possible that most of the episodes observed in our study would have been completely neglected by the subjects (who considered some form of swelling almost normal after sitting for so long).

A recent report¹⁵ suggests that in more prolonged flights (24 hours), 10% of passengers may be affected by symptomless DVT. This study also documented the positive, preventive effects of compression stockings. Further studies are required to evaluate the incidence of DVT, cost and

Table I. Results of the LMWH vs aspirin randomization study.

Groups	DVT Incidence	M:F
Control		
17 dropouts, 83 subjects, 166 limbs	4 (4.82%) subjects 6 (3.6%) limbs* (2 in both limbs) (+2 superficial thromboses)	2:2 2:1
Total	6+2 = 8 events in 166 limbs (4.82%)	
Aspirin		
16 dropouts; 84 subjects, 168 limbs	3 (3.6%) subjects [†] 3 (1.8%) limbs* (all one-side) (+3 superficial thromboses)	3:3 2:1
Total	3 + 3 = 6 events in 168 limbs (3.6%)	
LMWH		
18 dropouts; 82 subjects; 164 limbs	0 (0%) subjects 0 (0%) limbs [‡] (+1 superficial thrombosis) 1 event in 164 limbs (0.61%)	0:1
Total		9:7

*Difference: $p < 0.05$; two superficial DVTs in different patients; in total six patients and eight limbs were affected. [†]25% reduction in DVTs per subject ($p < 0.05$). [‡]Difference: $p < 0.002$; only one superficial thrombosis in 164 (0.61%) limbs.

benefits of prophylaxis with compression stockings or drugs, and the efficacy of other measures (i.e., educational programs). The evaluation of the occurrence of pulmonary embolism requires larger numbers of subjects and more prolonged observations.

These observations indicate that prevention with one dose of LMWH is effective in controlling DVT in high-risk subjects. Aspirin prophylaxis caused a 25% decrease in DVT incidence but in total the number of thrombotic events was 3.6% higher when compared with results in the LMWH group. Therefore, more evidence is needed for this form of prophylaxis; dosages should be better evaluated. One single dose of LMWH was associ-

ated, in this study, with the absence of DVTs and almost abolished all thrombotic events. Considering these preliminary observations, the use of a single dose of LMWH is an important option in high-risk subjects during long-haul flights if there are no contraindications.

In conclusion, DVT in long-haul flights may be an important safety issue^{1,15,21-24} that may be addressed by travelers, travel agents, airline companies, insurance companies, airport authorities, health authorities, and general practitioners. The World Health Organization recently organized a meeting to discuss the problem and potential strategies for evaluating the rate of DVT in a larger passenger sample and the effects of prevention

(March 2001). The incidence of DVT, particularly in high-risk subjects, may be high and therefore prophylaxis is advisable. On the basis of initial data, elastic compression stockings are the easiest and least problematic (no side effects) solution for prophylaxis. In high-risk subjects, a single dose of LMWH (enoxaparin) is effective in decreasing DVT risks. Aspirin, at least in our sample and with the prescribed dosage, may have a limited efficacy. It should be better evaluated, but exposes some patients to gastrointestinal side effects. Exercise during flights, diet suggestions, less baggage on board to increase leg space, and larger empty spaces on planes may help as well as suggestions from physicians not to travel (or travel differently) in conditions of particularly high risk. Patients with a history of thrombosis are at particularly high risk for new episodes (56% of patients with a documented DVT in this study had a possible, previous episode of thrombosis).

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