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Prevention of Venous Thrombosis in Long-Haul Flights with Flite Tabs: The LONFLIT-FLITE Randomized, Controlled Trial

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The aim of this study was to evaluate the development of edema, and superficial and deep vein thrombosis (DVT) prophylaxis with an oral profibrinolytic agent (Flite Tabs, 150 mg pinokinase, Aidan, Tempe, AZ, USA) in long-haul flights (7-8 hours), in high-risk subjects. A group of 300 subjects was included; 76 were excluded for several problems including concomitant treatments; 204 were randomized into 2 groups (active treatment or placebo) to evaluate the effects of prophylaxis with Flite Tabs. An exercise program was used in both groups. The femoral, popliteal, tibial, and superficial veins were scanned with ultrasound before and within 90 minutes after flights. Of the included subjects, 92 of 103 controls and 94 of 101 treated subjects completed the study. Dropouts were due to connection problems. Age, gender, and risk distribution were comparable in the groups. In the treatment group, no DVT was observed. In the control group, 5 subjects (5.4%) had a DVT and there were 2 superficial thromboses (7 events in 92 subjects; 7.6%). At inclusion, edema was comparable in the 2 groups. After flights there was an increase in score in controls (+12%) in comparison with a decrease (-15%) in the Flite Tabs group (the difference in variation was statistically significant). Intention-to-treat analysis for thrombotic events shows 18 failures in controls (11 lost to follow-up + 7 thrombotic events) of 92 subjects (19.6%) in comparison with 7 failures (of 94 subjects, equivalent to 7.4%) in the treatment group (p<0.05). Events were asymptomatic. In conclusion, Flite Tabs were effective in reducing thrombotic events and in controlling edema in high-risk subjects in long flights.

Introduction

Prolonged air travel has been associated with deep venous thrombosis (DVT) and pulmonary embolism (PE). Prolonged bending and compression of veins (i.e., popliteal, soleal veins) on the edges of the seat could be a contributing factor to stasis and thrombosis. Blood concentration, decreased fluid intake, and a dry atmosphere in cabins have been implicated. Blood changes have been reported during simulated
and real long flights, including fibrinogen and fibrinolysis alterations. Immobility, lower air pressure, and relative hypoxia alter fibrinolytic activity and cause release of vein wall factors, leading to stasis and thrombosis. Evidence now suggests that there is an association between DVT and long flights. The prevalence of DVT is higher in high-risk subjects. Measures to prevent DVT include advice to passengers (standing, stretching, exercising, drinking water, avoiding constrictive clothes). Subjects with risk factors for DVT; i.e., history of DVT, hormonal treatment, malignancy, recent surgery—should discuss additional, protective measures with their doctors including postponing the flight. Preventive measures include elastic stockings and antithrombotic prophylaxis with low-molecular-weight heparin (LMWH). In the LONFLIT studies, the incidence of DVT in high-risk subjects was greater than 4%. The LONFLIT 2 study—a prospective evaluation of DVT prevention with stockings—has shown that stockings decrease DVT incidence in long-haul flights. The Lonflit 3 study has shown a reduction in DVT in high-risk subjects with LMWH.

Flite Tabs (Aidan, AZ, USA) contain pinokinate, a new pharmacologic compound that includes a component improving fibrinolysis and a component controlling edema. The aim of this study was to evaluate the preventive effects of Flite Tabs in long-haul flights (7-8 hours) in subjects at high risk for DVT.

Patients and Methods

Three hundred subjects at high-risk for DVT were contacted and pre-included after informed consent; 76 subjects were excluded on the basis of several considerations: use of anticoagulant or anti-thrombotic drugs (22 subjects), cardiovascular treatments (34), other treatments (11), and possible low compliance (9). We included 224 subjects (114 in control group, 110 in the treatment group). The subjects were randomized into 2 groups to evaluate prophylaxis with Flite Tabs in 7- to 8-hour flights (New York–London or London–New York). High-risk criteria for DVT are those previously indicated in LONFLIT studies 1, 2 and 3, such as previous episodes of DVT or superficial vein thrombosis, coagulation disorders, severe obesity or limitation of mobility due to bone or joint problems, neoplastic disease within the previous 2 years, clinical cardiovascular disease, large varicose veins. Subjects taller than 190 cm and heavier than 90 kg were excluded.

Ultrasound scanning protocol (before/after flights). Sonosite scanners with a 7.5–13 MHz, high-resolution, linear probe (Sonosite, Bothell, WA, USA) were used to study the venous system by compression of the major veins (femorals, popliteal and tibials and the superficial veins).

Scanning Plan

Scanning was performed within 90 minutes before the flight and just after the flights (within 90 minutes).

Exclusion criteria were clinical diseases requiring medical treatment, severe bone/joint problems or limited mobility, uncontrolled diabetes mellitus, severe hypertension, obesity, recent thrombosis (less than 6 months), presence of thrombi, and increased D-dimer level at the pre-flight examination.

An Independent Study

The study organized by the LONFLIT Consortium was not sponsored by companies producing the materials quoted in this article.

Exercise Plan

Suggestions to passengers were given to both groups. The exercise plan was shown in a video to all subjects explaining DVT and its prevention. It consisted of mild exercise (mainly isometric) including standing and moving legs for 5 to 10 minutes every hour, avoiding baggage between seats, and drinking water regularly (100–150 mL of water every hour).

Testing

D-dimer and fibrinogen tests were performed before (within 12 hours) flights and within 4 hours after the flight (Dade Dimertest, Latex Test, Boehringer, Germany). As an inclusion standard, D-dimer was within normal values (< 200 ng/mL) before inclusion in all subjects.

Evaluation of Edema

A combined edema score (Table 1) was developed to assess in a quantifiable and reproducible way edema and swelling. The score is
Table I. Parameters and items considered in the evaluation of edema.

<table>
<thead>
<tr>
<th>Scale</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Edema test</td>
<td>0–&lt;1</td>
<td>&gt;1–2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>2 Ankle circumference (cm)*</td>
<td>0–1</td>
<td>&gt;1–2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>3 Volume (mL)*</td>
<td>0–2</td>
<td>&gt;2–5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>4 Subjective swelling</td>
<td>1–10</td>
<td>1–2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>5 Discomfort</td>
<td>1–10</td>
<td>1–2</td>
<td>&gt;2</td>
</tr>
</tbody>
</table>

Max. score: 0, 5, 10

Worst case, 10; no edema, 0.
*Difference before – after.

based on combined evaluation of parametric data (edema tester, variations in ankle circumference in centimeters, volume measurements in milliliters or in percent variation of the baseline volume) combined with the subjective assessments of swelling and discomfort measured on an analogue scale line. Items 4 and 5 are based on a scale line (range 0 to 10) defined by the study subjects before and after the flights. The edema tester (ACI-Medical, CA, USA) is a device developed to assess edema in a semi-quantitative way. The device is applied at the internal perimalleolar region underneath a sphygmomanometer, with its distal edge 2 to 3 cm proximal to the medial malleolus; pressure is applied for 3 minutes (constant pressure of 50 mm Hg). Pressure on the tester produce skin marks that are related to the presence and quantity of edema at the perimalleolar region. The edema tester had been studied and validated and previous studies indicate good reproducibility in standardized conditions. Ankle circumference was measured with a tape at the smallest ankle diameter. This method can measure with accuracy differences in variations of size greater than 1 cm. Volume variations are measured with water displacement (a Plexiglas leg-shaped chamber with a parallel 2 mm diameter tube connected with the main water chamber). This method can accurately measure water displacement (and its variations due to increased leg volume) with a range of accuracy of < 2 mL. The maximum calf size is carefully measured before volume measurements and marked onto the skin. The leg is immersed in water and the water level—and its displacement—are measured at the maximum calf circumference. The leg volume before the flight is arbitrarily considered to be 100% and any increase in volume is therefore measured as a percentage.

Flite Administration

Flite Tabs contain 150 mg of pinokinase, which is a proprietary blend of Pycnogenol® and Nattokinase. Other ingredients are rice flour and gelatin capsule. Subjects took 2 capsules 2 hours before flights with 250 mL of water and 2 capsules 6 hours later with 250 mL of water. Placebo capsules were administered accordingly to the control group with the same amount of fluid. The constituents of pinokinase have anecdotally reduced symptoms associated with traveling on long-haul flights greater than either ingredient alone. Those symptoms included lower extremity edema, aching, and discomfort. Nattokinase has documented fibrinolytic activity, and Pycnogenol has been demonstrated to reverse symptoms of venous insufficiency. The study hypothesis was that the combination of the two ingredients may reduce edema and symptoms, and prevent DVT in high-risk individuals. Nattokinase is a fibrinolytic enzyme purified from the fermented soybean food Natto, which has been consumed orally for at least 400 years (it is produced by fermenting soybeans with the bac-
terium Bacillus subtilus). B. subtilus has been given GRAS (Generally Regarded as Safe) status in the United States and has been marketed as a natural biologic control product in many countries. Oral administration of nattokinase produces a significant enhancement of the fibrinolytic activity in the plasma, as indicated by measurement of fibrinolytic parameters and the endogenous product of tissue plasminogen activator.

Pycnogenol is a water extract from the bark of the French maritime pine; it represents a natural blend of constant proportions of bioflavonoids including catechin, epicatechin, taxifolin, oligomeric proanthocyanidins, and phenolic fruit acids (ferulic acid and caffeic acid). Clinical studies on more than 2,000 patients have shown, very rarely, only mild side effects such as gastrointestinal upsets.

Statistical analysis was performed with non-parametric tests (Mann-Whitney U-test) and the analysis of variance considering event-free subjects completing the protocol. The specific incidence of thrombotic events (DVT or superficial thrombosis) was calculated and compared considering individuals and by intention-to-treat analysis.

### Results

All subjects underwent scanning within 90 minutes before the flight and within 90 minutes after disembarking (average 44 minutes; SD 18). Flight duration was on average 7 hours and 44 minutes (SD 34 minutes). Of the 103 included subjects in the control group and 101 in the treatment group (204 total), 92 controls and 94 treated subjects (186 total) completed the study. Dropouts were due to low compliance to the protocol or flight-connection problems. Age/gender distributions were comparable in the 2 groups.

### Controls

Of the 92 subjects in the control group (mean age 49.8; SD 13; range 29–68; M:F = 46:46), 5 subjects (5 limbs) had a DVT and 2 (2 limbs) a superficial thrombosis (Table II). The incidence of thrombotic events was 7.6%.

### Flite Group

Of the 94 subjects in the treatment group (mean age 48; SD 12; range 27–69; M:F = 48:45), no

### Table II. Results table.

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>Treat</th>
<th>Total</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected subjects</td>
<td>114</td>
<td>110</td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>Included</td>
<td>103</td>
<td>101</td>
<td>204</td>
<td>ns</td>
</tr>
<tr>
<td>Completing the Study</td>
<td>92</td>
<td>94</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td>Lost</td>
<td>11</td>
<td>7</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>SVT</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Events (%)</td>
<td>7.6</td>
<td>0</td>
<td>7.6</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>ITT* (failures)</td>
<td>18/92</td>
<td>7/94</td>
<td>25/186</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>%</td>
<td>19.6</td>
<td>7.4</td>
<td>13.44</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Of the 300 pre-selected subjects, 224 were actually included (76 were excluded for several reasons); 186 completed the study (18 were lost at the end of the flight for non-medical problems, mainly connections).  
*ITT*: Intention to treat analysis detects 18 failures in the control group (11 lost to follow up + 7 thrombotic events) out of 92 subjects (19.6%) versus 7 failures (7.4%, all lost, no events) in the treatment group (p < 0.05).
thrombotic event was observed. The difference in events incidence between the groups is significant (p < 0.025).

Intention-to-treat analysis detects 18 failures in the control group (11 lost to follow-up + 7 thrombotic events) out of 92 subjects (19.6%) in comparison with 7 failures out of 94 subjects (7.4%) in the treatment group (p < 0.05).

Side Effects, Tolerability

The tolerability of Flite Tabs was very good and there were no major complaints or side effects. No subject stopped the prophylaxis plan. All thrombotic events were asymptomatic. The compliance to treatment was very good (98% of the capsules were correctly used).

Testing

D-dimer test results were within normal values (< 200 ng/mL) before inclusion. The test at arrival was not possible in 6 subjects (for connections problems). All tests were performed within 2 hours after the flight (average 69 minutes; SD 23 minutes). Tests were within the normal range after the flight and no significant difference between mean values measured in subjects with ultrasound-detected DVT and those without DVT was observed. The test can be performed in a few minutes and it has no cross-reactivity with fibrinogen or its breakdown products. Fibrinogen values were within the normal range before and after the flights and there were no significant differences between non-thrombotic and thrombotic subjects after the flight.

Analysis of Thrombotic Events

The 4 females who had a thrombotic event in the control group (3 DVT, 1 SVT) were taking low-dose oral contraceptives. The treatment had been used for at least 8 months before the flight. No statistically significant difference was observed in the events distribution between men and women (3 to 4; 3 DVT, 1 SVT in women).

Edema Evaluation

Edema at inclusion was comparable in the 2 groups (Table III, Figure 1). After flights there was an increased score in controls (+12%) in comparison with a decrease (−15%) in the treatment group. The difference in variation was significant (p < 0.02). In the control group, 89% of subjects had a clear increase in ankle circumference and volume which was clinically evident and associated to some degree of discomfort. The control of edema with Flite Tabs was significant considering parametric data (circumference, volume) and nonparametric (analogue scale line) observations. In included subjects the average maximum calf size was 39.4 cm (SD 2) cm in men and 33 cm (SD 1.1) in women. The height of the maximum diameter was 38 cm (SD 1.1) in men and 34 cm (SD 1) in women. The average volume before flights was 2,212 mL (SD 19) in men; 1,998 mL (SD 12) in women. The minimum ankle circumference was 22.2 (2) cm in men and 18.6 (2) in women. Subjects selected for the study were average for weight and height.

The presence of DVT was associated with edema at the end of the flight. It is possible that...
Table III. Edema variation.

<table>
<thead>
<tr>
<th>Score</th>
<th>Treatment</th>
<th>Control</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>8.88 (SD 1.2)</td>
<td>8.7 (SD 1)</td>
<td>ns</td>
</tr>
<tr>
<td>After</td>
<td>7.54 (SD 0.8)</td>
<td>9.8 (SD 0.5)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>% Variation</td>
<td>-15</td>
<td>+12</td>
<td>p&lt;0.02 (27%)</td>
</tr>
</tbody>
</table>

The development of edema was a relevant factor in producing DVT causing vein compression.

In conclusion, Flite Tabs are effective in reducing the incidence of flight-related DVT, in high-risk subjects, in 7- to 8-hour flights.

Conclusions

Travel/flight-related DVT is a preventable disease. Most after-flight DVTs are neglected because they are often (89%) asymptomatic. A report suggests that in prolonged flights (24 hours), approximately 10% of passengers may be affected by DVT. Further studies are required to better evaluate the incidence and social epidemiology of flight-related DVT, costs and benefits of prophylaxis. The main cause of the problem—swelling and DVT—are caused by the limited space available in flights on aircrafts. American Airlines has recently increased the distance between seats in all sections of their planes. This has probably caused an important reduction in DVT and other complaints due to vascular problems (LONFLIT studies, data on file). Edema and swelling are the results of restricted motion, immobility in association with decreased pressure in the cabin environment, leading to vein dilatation. These factors may be aggravated by venous disease, diabetic microangiopathy and other conditions causing edema (i.e. cardiac and renal insufficiency and antihypertensive treatment). Exercise is helpful but not sufficient. In some subjects, edema compressing minor veins could be an initial cause of DVT. Therefore controlling edema is important to decrease the incidence of DVT. In our study, D-dimer and fibrinogen were not effective in detecting events or in forecasting thrombotic events.

In conclusion, DVT in long flights is an important issue. The incidence of DVT in high-risk subjects may be high, according to risk level and flight length and different conditions (4%-10%). Prophylaxis is advisable, particularly for high-risk subjects. Elastic stockings are an effective solution for prophylaxis. In higher-risk subjects, enoxaparin is effective in decreasing risk of DVT, at a relatively higher cost and with a limited risk of side effects. Exercise during flights—if and when possible—diet suggestions, less baggage on board (to keep free leg space), and larger empty spaces on planes may help. Suggestions from physicians not to travel or to travel in a different way are very important in conditions of particularly high risk. All patients with a recent history of thrombosis, or with chronic venous insufficiency are at higher risk of DVT. The average population flying on planes is different from our selected samples (i.e., we have excluded subjects with cardiovascular disease requiring drug treatment, those particularly handicapped or very old) and may be prone to more thrombotic events. Therefore these results, when extrapolated to the general flying population may find a higher incidence of thrombotic events and a better cost-efficiency ratio of prophylaxis. Flite Tabs may offer a very important option for prophylaxis without increasing risks. The pro-fibrinolytic prophylaxis and the anti-edema effect may also be combined to compression with stockings in particularly high-risk subjects.

New observations define better that the risk of flight-DVT is not minimal. Recent studies indicate new possibilities of prevention. New epidemiologic studies are very important, particularly to define risk distribution. Guidelines on these problems are available but should be rewritten on the basis of more recent observations. It is possible that most of the signs and symptoms of swelling observed in our study...
would have been completely neglected by the study subjects who considered some form of swelling almost normal after sitting for so long.

Edema and swelling are the results of immobility in association with the decreased air pressure in the cabin environment. They may be aggravated by the presence of venous disease, diabetic microangiopathy, and other conditions causing edema (i.e., cardiac and renal insufficiency and antihypertensive treatment). In some cases edema, compressing minor veins may be an important initial cause of DVT (classified, unpublished data from the LONFLIT studies).17-19 Controlling edema is theoretically important to decrease the incidence of thrombotic events. Patients with a history of thrombosis and chronic venous insufficiency are at particularly higher risk45 of developing new episodes; 56% of patients in the LONFLIT3 study17-19 with a documented DVT had had a possible episode of thrombosis. This study also indicates that edema, which is common and observed in almost all subjects, even those with healthy circulation, could be an important prevention issue.

Our recent prevention study (Jap study)54 indicates that in longer flights there is a significant risk of thrombotic events in high-risk individuals (5%-7%) and that most thrombotic events may be prevented by compression. The BEST study55 reports conflicting results with no observation of DVT but an increase in D-dimer in a percentage of subjects. However, risk categories in this study were not separated and there was no prophylaxis. Venous disease, edema, and DVT56,57 are very common observations and some 35% of subjects flying for longer than 10 hours may have venous disease or some type of edema.54,56,57 The classification of risk categories for venous thrombosis58,59 is well defined, but it is possible that for conditions such as long-flights risk categories may be adjusted to different standards. Recently the occurrence of a high incidence of DVT (with some episodes of pulmonary embolism) in pilgrims traveling by bus has been observed60 expanding the magnitude of the problem. Pycnogenol is a powerful anti-edema compound and increases capillary wall resistance, makes them less permeable, contributes to the control of edema, and has anti-inflammatory effects.51 Its efficacy has been confirmed on the basis of objective and subjective signs and symptoms of edema in venous insufficiency.62 Natto is also a very interesting compound, well known in Japan, but less used in Europe and in the United States with documented profibrinolytic activity.53-66 Flite Tabs, including both compounds, are an interesting combination, effective in this study in preventing thrombosis. This new part of the LONFLIT study indicates an important protective effect of Flite. These results, when extrapolated to the general flying population, may be more important and significant. Flite Tabs offer an important preventive option, without increasing risk (i.e., due to the use of drugs) or costs.

REFERENCES


