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ORIGINAL ARTICLE

Long-haul flights, edema, and thrombotic events: prevention with stockings and Pycnogenol® supplementation (LONFLIT Registry Study)

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ABSTRACT

BACKGROUND: This registry study evaluated the effects of Pycnogenol® on edema and thrombotic complications in long-haul flights; jet lag was also evaluated.

METHODS: Four hundred and fifty subjects at different risk levels for thrombosis, flying in economy class twice in less than a week for more than 8 hours, were included; 295 completed the registry study and were subdivided in 3 groups according to their risk level — low, moderate, or high. The high-risk group also received Aspirin®. A standard management (SM) was used in all groups. In each risk category, three groups were made according to patient management: a Pycnogenol® group, a SM group (control), and a stockings group. The groups were comparable at inclusion. No side effects were observed.

RESULTS: In the low risk group edema were reduced more (P<0.05) with Pycnogenol® and stockings compared to control. Ankle circumference was smaller with Pycnogenol® (P<0.05). No thrombosis was detected. D-dimer was negative in Pycnogenol® subjects; one subject in the control group had increased values, as did two of the 36 subjects in the stockings group. In the group with moderate risk, edema and ankle circumference were lower in the Pycnogenol® group (P<0.05). One deep vein thrombosis (DVT) and one minimal superficial vein thrombosis (SVT) was seen in controls. D-dimer was normal in the Pycnogenol® group. In high-risk subjects, edema, and ankle circumference were significantly reduced in the Pycnogenol® group (P<0.05). There were no SVT or DVT in the Pycnogenol® group. One minimal DVT and one SVT were observed in controls. D-dimer was negative in all Pycnogenol® subjects (P<0.05); three post-flight values increased in controls and in four of the 32 subjects in the stockings group. The jet lag score was lower in low-, medium-, and high-risk Pycnogenol® subjects (P<0.05).

CONCLUSIONS: This registry study indicates that Pycnogenol® supplementation reduces edema and may control some thrombotic events.

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Key words: Pycnogenols - Compression stockings - Antifibrinolytic agents.

Prolonged air travel has been associated with deep venous thrombosis (DVT) and pulmonary embolism (PE).[1-8] Prolonged bending and compression of leg veins (*i.e.*, femoral, popliteal, soleal veins) on the edges of the seat could be a contributing factor to stasis and thrombosis.[9-14] An increase in blood cell concentration, decreased fluid intake and the dry and low-pressure environment in cabins have been implicated to increase risk of thrombotic events.[7-9] Blood changes have been reported during simulated and real long flights, including

fibrinogen and fibrinolysis alterations.[10, 11, 14] Immobility, lower air pressure, and relative hypoxia may alter the spontaneous fibrinolytic activity and cause release of factors, leading to thrombosis.[12-14] Evidence suggests that there is a significant association between DVT and long flights.[14-19] The prevalence of DVT is higher in predisposed, high-risk subjects.

Measures to prevent DVT include advice (changing positions, stretching, exercising, drinking, avoiding constrictive clothes). Subjects with risk factors for DVT; *i.e.*, history of DVT, hormonal treatments, malignancy, recent surgery, should avoid, if possible, long flights and discuss protective measures with their physicians including postponing the flight.[14, 17-20] Effective preventive measures include elastic stockings and antithrombotic prophylaxis with low-molecular-weight heparin (LMWH) or anticoagulants [14-18] in very high-risk conditions.

In the LONFLIT studies,[14, 15] the incidence of DVT in high risk subjects was greater than 4%. The LONFLIT 2 study — prospective evaluation of DVT prevention with stockings [14] — 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 using low-molecular-weight heparin (LMWH).[16-18] A specific product (Flite Tabs, Aidan, AZ, USA) including a combination of Pycnogenol® and nattokinase (an oral profibrinolytic agent) has been also useful to reduce edema and minor thrombotic events.[21, 22]

The aim of this registry study was to evaluate the development of edema and vein thrombosis (DVT) in subjects with different levels of risk for thrombosis, using prophylaxis with an oral supplement (Pycnogenol®) in long-haul flights (>8 hours).[23-28]

Healthy subjects were included into 3 groups (using Pycnogenol® or stockings and a control group) to evaluate the effects of the edema prophylaxis. An in-flight exercise program and hydration were used as a standard management (SM) in all groups. The femoral, popliteal, tibial and superficial veins were scanned with ultrasound before and within 24 hours after the final flights.

This supplement registry was organized to evaluate the effects of Pycnogenol® (French maritime pine bark extract) on edema, swelling and minor thrombotic complications in long-haul flights. A secondary aim was the evaluation of the effects of Pycnogenol® supplementation on jet lag symptoms.

Materials and methods

Four hundred and fifty subjects at different levels of risk [26, 27, 29] for edema and DVT were contacted and pre-included after informed consent, 295 (143 females) completed the full study period (Table I). The other subjects could not participate on the study due to logistical problems. The subjects were flying in economy class for more than 8 hours, twice in less than a week. There were no drop-outs. The subjects were divided into 3 risk classes — low, moderate, and high. The high-risk group also received Aspirin. Based on personal preference, these three risk categories were further subdivided into three treatment groups:

— a Pycnogenol® group, using Pycnogenol® plus SM;

— a control group, following SM;

— a stockings group, using below-knee, Sigvaris (Wintertur, Switzerland) 702 elastic stockings (with an average ankle pressure of 20-30 mmHg) plus SM.

The definition criteria for high risk of DVT considered in the present study are those described in the LONFLIT studies 1, 2, and 3.[14-20] Normal, asymptomatic subjects can be subdivided into risk levels (low, moderate, high) for thromboembolism according to their medical history, general risks (weight, metabolic conditions, mobility, etc.), presence of thrombophilic factors, environmental conditions (including type of surgery or immobility, or long flights).

Subjects taller than 190 cm and heavier than 90 kg were excluded.[21-25]

Tests

Before and after the flights, subjects were evaluated with thermography (including both limbs) using a Flir 440 Camera (FLIR, Swe-

TABLE I.—*Groups of subjects from the LONFLIT06 study.*

	Low-risk group			Moderate-risk group			High-risk group		
	Pycno	Controls	Stockings	Pycno	Controls	Stockings	Pycno	Controls	Stockings
Screened patients (N.=450)	50	50	50	50	50	50	50	50	50
Completing patients (N.=295)	33	36	36	32	38	38	25	25	32
Sex, females	15	16	17	17	18	18	14	13	16
Age	43.4;3	44;2.2	44;2.2	45;2.3	43.3;3.1	43.2;1.6	44.2;1.9	43.6;1.8	43.2;2
Edema (score 1-4)	1.03;0.2*	2.4;0.2	2.1;0.3	1.7;0.3*	3.6;0.2	3.4;0.2	1.6;0.4*	3.4;0.2	3.4;0.2
Ankle circumference, cm	22.4;0.3*	23.3;0.3	22.6;0.3	22.3;0.2*	23.9;0.4	23.2;0.6	22.6;0.2*	23.8;0.1	24;0.2
DVT duplex	–	–	–	–	1 (minimal)	–	–	1	–
SVT duplex	–	–	–	–	1	–	–	1	–
Thermal hot-spots	–	–	–	–	2	–	–	3	–
D-dimer, negative	33/33*	35/36	34/36	32/32	36/38	35/38	25/25*	22/25	28/32
Fibrinogen, g/L	1.5;0.4	1.52;0.1	1.63;0.3	1.88;0.2	1.94;0.3	1.9;0.3	1.4;0.2*	1.92;0.3	1.9;0.1
Leg pain and discomfort (score 1-4)	1.2;0.1*	2;0.2	2;0.2	1.5;0.1*	2.4;0.1	2.4;0.2	1.5;0.3*	2.5;0.1	2;0.2
Overall J-LAG (score 1-4)	0.9;0.1*	1.8;0.2	2.1;0.3	1;0.1*	2.9;0.2	3.2;0.2	1.1;0.2*	2.9;0.1	3.2;0.2

Flights: at least 10 hours; economy class; standard management for all subjects; BMI<26 kg/m^2.
Fibrinogen, normal levels: 1.5-3 g/L; D-dimer, normal levels <0.5 mg/L or µg/mL.
Stockings: Sigvaris Elas Stock.
*Statistically significant difference to control (P<0.05).

den). D-dimer tests and ultrasound scanning were performed before and after the flights. Sonosite scanners with a 7.5-13 MHz, high-resolution, linear probes (Sonosite, Bothell, WA, USA) were used to study the venous system by compression of the major veins (femoral, popliteal, soleal, tibial, and superficial veins).[26, 27]

Scanning was performed within 24 hours before the flight and within 30 hours after the second, return flight.

Exclusion criteria were clinical diseases requiring any medical treatment, severe bone/joint problems. Also, problems limiting mobility, diabetes, mellitus, severe hypertension, obesity, recent thrombosis (<6 months) and increased D-dimer level at the pre-flight examination were criteria of exclusion. All subjects in the high-risk group were using an ACE-inhibitor for moderate, non-complicated essential hypertension and were therefore considered more prone to distal edema.

An Independent Study. Companies producing the materials quoted in this article did not sponsor the registry study, which was organized by the LONFLIT Consortium.

Supplement studies

Supplement registry studies [28-30] define the field of activity of standardized supplements and possible preventive, preclinical applications. The best fields of application for standardized supplements are preclinical, borderline applications or the supplementary management of risk conditions. Supplements, unless there are specific claims, are not generally used for treatment of clinical conditions. They may be used to manage minor medical problems and conditions. Supplement studies produce supplementary data to be compared to "background" historical data (*i.e.*, based on the best available management for comparable subjects) or to other management plans. In this study the supplement was used according to the following rules:

— the use of the supplement should not have interfered with any other treatment, management or preventive measures;

— the period of follow-up is considered variable, according to the needs and availability of the registry subjects. The observation period is therefore variable, not fixed in advance. Ideally, the supplement should be used as long as needed to see results or changes;

— the type of evaluation for these studies is always a registry. The evaluation of the compliance concerning the use of the supplement indicates how many subjects are willing to use the product;

— in supplement studies there is no defined group allocation, no randomization organized

by the investigators. Subjects decide — on the basis of an initial briefing — which management group they wanted to join including the control (non-supplement) group. No placebo is used.

SM plan

Suggestions for the flight were given to all subjects. The basic exercise plan was shown in a video (and in the flight magazine) explaining DVT and its prevention. The plan included exercise (mainly isometric: standing and moving legs for 5 to 10 minutes every hour, avoiding constrictive clothes and baggage between seats, and drinking water regularly (100-150 mL of water every hour).[31-36]

Evaluation of edema after the flight.[35-38] A combined edema score (Table I) was used to assess quantitatively edema and swelling. The score is based on combined evaluation of data based on subjective assessments of swelling and discomfort measured on an analogue scale line. 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 0.4 cm at the ankle.

Pycnogenol® (150 mg/day equivalent to 3 cps/day was started 3 days before the flights and stopped 3 days after the second flight. Pycnogenol® (Horphag Research) is a product of natural origin (French maritime pine bark) with a high level of standardization [39-41] that has been shown to control edema and symptoms associated to venous insufficiency [23, 24, 32, 38, 42] in several preclinical and clinical conditions.

D-dimer (Dade Dimertest, Boehringer, Germany) was measured before (within 24 hours) flights and within 24 hours after the second flight in all subjects.[15, 18, 43, 44] D-dimer was within normal values before inclusion.

The main study hypothesis was that reducing edema and swelling may help preventing thrombotic events in high-risk individuals.

Jet lag [31, 32, 35, 36] is also frequent in long-haul passengers (particularly in those who are more prone to edema, such as subjects on anti-hypertensive drugs) and when flight conditions (including crossing several time zones) are associated. The evaluation of the most frequent observations in jet lag were evaluated with a specific analogue visual scale line (Table II).[36]

TABLE II.—*LONFLIT06 Jet lag questionnaire including cognitive function.*

	Pycnogenol	Stockings	Controls
Sleep quality deterioration	1.3;0.2*	2.6;0.2	2.6;0.2
Desyndromization	1.8;0.3*	2.7;0.1	2.4;0.1
Deterioration in attention	1.9;0.3*	2.3;0.2	2.3;0.2
Tiredness/fatigue	2.4;0.4*	3.2;0.2	3;0.2
Visual impairment	1.6;0.2*	2.3;0.3	2.3;0.2
Impairment in cognitive function	1.4;0.1*	2.5;0.2	2.8;0.4

Score (0-4) after the second flight (average of 2 flights).
*P<0.05 in comparison with the other two study groups.

Statistical analysis

Statistical analysis was performed with all nonparametric tests (ANOVA, 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 evaluated in previous comparable studies. The evaluation of the visual analogue scale lines according to Maxwell.[45]

Results

A group of 450 subjects, equally divided into three groups (low, moderate and high risk) were screened and judged adequate (and willing to participate) for the observational, prevention study. The number of subjects actually completing the two-flight registry study according to plans is given in Table I. There were no drop-outs, the difference in patients (between selected and completing subjects) was due to logistical reasons and impossibility to be re-evaluated after the final flight. Subjects completing the study according to plans resulted comparable in the different groups (Table I).

No side effects or tolerability problems were observed with the supplement or with stockings.

Low-risk category

The subjects in the three management groups were comparable. Edema after flight (Table I) was significantly lower (P<0.05) with Pycnogenol® and stockings than in the SM group; Pycnogenol® was more effective than stockings (P<0.05). Ankle circumference was smaller in the Pycnogenol® and stockings groups than in control subjects (P<0.05). In low-risk subjects, no DVT and no SVT were detected.

Thermal imaging revealed no hot spots indicating the absence of an inflammatory of thrombosed area.

D-dimer was negative in all Pycnogenol® subjects; in the control group, only one subjects of 36 had a mild increase; in the stockings group, 2 of 36 subjects had higher D-dimer levels. The average fibrinogen level showed minimal variations in this category of subjects.

Leg pain was more frequent in controls and subjects using stockings than in the Pycnogenol® group (P<0.05). In addition, discomfort (rated on a visual scale from 1 to 4) was lower in subjects using Pycnogenol® (P<0.05).

Moderate-risk category

The 3 management groups were comparable at inclusion. After the flights, edema was significantly smaller in the Pycnogenol® group (P<0.05), yielding a better effect than stockings. Pycnogenol® was significantly more effective in the evaluation of ankle circumference in comparison with controls and subjects using stockings (P<0.05). Only one limited DVT and one SVT (minimal, limited; <0.5 cm in extension in the long saphenous vein) were observed in controls.

Two clear thermal spots were seen in controls corresponding to the limited thrombotic events.

D-dimer in all subjects at inclusion was <0.5 mg/L or µg/mL (normal range). After the flights, D-dimer was negative — within the normal range — in all Pycnogenol® subjects; in two control subjects the test was increased and in 3 out of 36 subjects in the group with stockings D-dimer was increased.

Fibrinogen before and after the flights showed only minimal variations, within the normal range in all subjects. It was lower (but the value was not significant) in the Pycnogenol® group.

Leg pain was more frequent in control subjects and with stockings (P<0.05). In addition, discomfort (rated on a scale from 1 to 4) was lower in the Pycnogenol® group compared to the other two study groups.

High-risk category

The three groups were comparable at inclusion. After the flights, edema was significantly lower with Pycnogenol® supplementation (P<0.05), compared to controls and to subjects using stockings. Ankle circumference with the supplement was significantly (P<0.05) smaller than in the control group and in the stockings group. One minimal, soleal (>0.5 cm) DVT and one well-defined SVT were observed in controls. There were no SVT or DVT in the Pycnogenol® group.

Three thermal spots (one vein inflamed and 2 with minimal thrombi) in controls were corresponding to the limited thrombotic events. No thermal spot was observed in the Pycnogenol® and stockings groups.

D-dimer was negative in all Pycnogenol® subjects, a better result than the other groups (P<0.05); 3 post-flight values were increased in controls, and in the stockings group, 4 subjects out of 32 had a higher value. Fibrinogen measurements showed minimal variations with a significantly lower value with Pycnogenol®.

Lastly, leg pain was more frequent in controls and in the stockings group (P<0.05). Discomfort was less frequent with Pycnogenol® (P<0.05). Stockings improved this symptom compared with controls (P<0.05).

Jet lag evaluation

Table I shows the variations in Jet lag global score (ranging from 1 to 4). In low-risk subjects, the score was significantly lower with Pycnogenol® (0.9;0.1, P<0.05) in comparison with controls (1.8;0.2) and with stockings (2.1;0.3). In moderate risk subjects, Pyc-

nogenol® subjects had a lower score (1;0.1, P<0.05) in comparison with the other two groups (controls 2.9;0.2, stockings 3.2;0.2). In high-risk subjects, the supplementation was associated to a better post-flight score (1.1; 0.2, P<0.05) in comparison with controls (2.9;0.1) and with subjects using stockings (3.2;0.2). Table II provides the results for all pooled subjects in the three study groups; each of the six main signs of jet lag was milder in the Pycnogenol® group (P<0.05).

The apparent parallel relieve in peripheral edema and jet-lag symptoms may be theoretically connected to a general edema reduction (particularly in high and moderate risk subjects, including subjects using anti-hypertensive treatment).

Previous studies have indicated that most subjects with significant jet lag symptoms have a "minimal" brain edema in the hours following long-haul flights which is only visible with CT scans. The resolution and disappearance of edema and the resolution of symptoms appear to be related and parallel in some defined cases.

In this registry study, no subject was forced to stop the prophylaxis plan, and none had to use other drugs (excluding the antihypertensive compound already in use).

All thrombotic events were asymptomatic and minimal, well localized. The compliance to prophylaxis was very good (98% of the supplement capsules or aspirin tablets were correctly used).

Discussion

Edema and DVT linked to long flights are preventable conditions in most subjects. [14-18, 46-48] Most post-flight DVTs are neglected because they are often (89%) asymptomatic [16-19] or very small. However, thrombi can grow and extend themselves in time.

Studies [31-34] indicate that in long flights some 10% of passengers at risk may be affected by DVT. The evaluation of incidence needs a larger evaluation considering flight times, conditions and costs/benefits of any form of prophylaxis.[31-38] Swelling and DVT may be associated to the limited space available in cabins.[46] Several companies have recently increased the space between seats in all sections of their planes. This may produce a reduction in the incidence of DVT/SVT.

Edema and swelling are also results of restricted motion, immobility in association with a lower air pressure in the cabin environment, leading to a possible, passive vein dilatation. These factors may be aggravated by the presence of venous disease, diabetic microangiopathy and other cardiovascular conditions associated to edema (*i.e.* cardiac and renal insufficiency and antihypertensive treatment).[31, 47-49] Exercise during flights is helpful but not always sufficient [17, 18] and, in subjects at risk, edema compressing minor veins could be an initial local cause of DVT.[34, 43, 46] The control of edema appears therefore important to decrease the incidence of DVT.

In the present study, D-dimer and fibrinogen were not very effective or practical in detecting or predicting minor thrombotic events at their initial stages. Blood test are not very effective in detecting DVT. There are conflicting results with increased D-dimer value but no detection of DVT in a percentage of subjects.[47-49]

Elastic stockings are considered an effective solution for prophylaxis. In high-risk subjects (*i.e.* after trauma or surgery), low-molecular weight heparin is effective in decreasing risk of DVT with limited risk of side effects.

Movement during flights — if and when possible —, diet adjustments, and more leg space on planes may help. Suggestions from physicians not to travel or to travel in a different way are very important in conditions of increased risk. Patients with a recent history of thrombosis, or chronic venous insufficiency are considered at higher risk of DVT.[31-33]

The average population flying on planes is different from our selected samples (*i.e.*, we have excluded subjects with severe cardiovascular disease requiring multiple drug treatment, those particularly handicapped or very old, subjects with heart failure): these subjects may be prone to more and more complex thrombotic events.

Aspirin is effective in arterial problems more than in venous problems; it has shown no

clear, significant efficacy in preventing flight-related DVT. In addition, tolerability problems must be considered; some 30% of patients may not be able to use aspirin. In longer flights, there is a significant risk of thrombotic events in high-risk individuals but most thrombotic events may be prevented by compression with specific elastic stockings.

In the Flite study,[27] the combination of Pycnogenol® (controlling edema) and nattokinase (improving spontaneous fibrinolysis) [21, 22, 27] was effective in decreasing the incidence of edema, swelling and some thrombotic events. This combination seems promising, and a study extension of this present study is currently evaluating the combination of nattokinase and Pycnogenol®.

Venous disease, edema, and DVT are common observations; some 30% of subjects flying for longer than 10 hours may have venous disease or some type of edema before the flight. The classification of risk categories for venous thrombosis is well defined,[18, 20] but it is possible that for conditions such as long-flights, risk categories may be adjusted to different standards. All patients should be educated to avoid flight-related complications.[47-50]

Jet lag [31, 32, 35] is also an important component of long flights and it is a model of altered attention and desynchronization. It appears that edema at the lower limb — often even observable at the hands — is matched by an increased level of edema at brain level. Minimal brain edema has been documented by CT scans after flights. Even a minimal quantity of edema may be associated to jet lag symptoms, including temporary desynchronization and loss of cognitive functions that improves with return to normal pressure and mobility, in hours. Subjects using antihypertensive products or drugs causing edema may be more prone to these symptoms. Pycnogenol® appears to control the minimal brain edema also improving jet-lag in most subjects. However, more observations are needed.

Conclusions

Pycnogenol® is a powerful anti-edema compound; it decreases capillary filtration (leading to edema) makes the capillaries less permeable, contributing to the control of edema and has a significant anti-inflammatory activity.[39, 42] Its safety and efficacy has been confirmed in this study considering objective and subjective signs and symptoms of edema.[30]

In conclusion, in this new LONFLIT study Pycnogenol® seems to effectively control edema, and there is indication that it may also contribute to control some early thrombotic events (but this requires an evaluation of a larger number of high-risk subjects).

Larger numbers of subjects are needed, and a new study is still in progress.

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