Clin Appl Thrombosis/Hemostasis 10(4):373–377, 2004

Prevention of Venous Thrombosis and Thrombophlebitis in Long-Haul Flights with Pycnogenol®

G. Belcaro, PhD, M. R. Cesarone, MD, P. Rohdewald, PhD, A. Ricci, MD, PhD, E. Ippolito, MD, M. Dugall, MD, M. Griffin, PhD, I. Ruffini, MD, G. Acerbi, MD, M. G. Vinciguerra, PhD, P. Bavera, MD, A. Di Renzo, MD, B. M. Errichi, MD, and F. Cerritelli, PhD

Department of Biomedical Sciences, Irvine2 Vascular Lab, G D'Annunzio University and San Valentino Vascular Screening Project (Pe), Faculty of Motory Sciences, L'Aquila University, Italy

Summary: The aim of this study was to evaluate the occurrence of deep venous thrombosis (DVT) and superficial vein thrombosis (SVT) and its prophylaxis with an oral anti-edema and antithrombotic agent (Pycnogenol®, Horphag, Research Management SA, Geneva, Switzerland) in long-haul flights, in subjects at moderate to high-risk of DVT and SVT. The study pre-included 244 pre-selected subjects; 211 were included (33 were excluded for several reasons due to logistic problems) and 198 completed the study; 13 subjects were lost for follow-up at the end of the flight, all for non-medical problems (i.e., for difficult connections). All subjects were scanned within 90 minutes before the flight and within 2 hours after disembarking. Subjects were supplemented with 100 mg Pycnogenol® per capsule. Treatment subjects received two capsules between 2 and 3 hours before flights with 250 mL of water; two capsules were taken 6 hours later with 250 mL of water and one capsule the next day. The control group received comparable placebo at the same intervals. The flight duration was on average 8 hours and 15 minutes (SD 55 min) (range, 7.45–12.33). In the control group there were five thrombotic events (one DVT and four superficial thromboses) while only non-thrombotic, localized phlebitis was observed in the Pycnogenol® group (5.15% vs. no events; $p<0.025$). The ITT (intention to treat) analysis detects 13 failures in the control group (eight lost to follow up + five thrombotic events) of 105 subjects (12.4%) vs. five failures (4.7%; all lost, no thrombotic events) in the treatment group ($p<0.025$). No unwanted effects were observed. In conclusion, this study indicates that Pycnogenol® treatment was effective in decreasing the number of thrombotic events (DVT and SVT) in moderate-to-high risk subjects, during long-haul flights.

Key Words: Venous thrombosis—Edema—Flight-microangiopathy—Noninvasive investigations—Ultrasound—Travel—Airplanes—Long-haul flights—Prevention—Fibrinolysis.

Prolonged air travel has been associated with deep venous thrombosis (DVT) and pulmonary embolism (1–6). Compression of veins (i.e., the popliteal vein) on the edge of the seat could be a contributing factor to venous stasis and DVT. Blood concentration, decreased fluid intake, and water loss in the dry atmosphere of airplane cabins, has been implicated (7–9). Biochemical changes have been reported during simulated and real long flights (10,11). Immobility, decreased air pressure, and relative hypoxia may alter fibrinolytic activity and cause release of thrombogenetic vein wall factors, leading to venous stasis or thrombosis (12–19), particularly in predisposed subjects.

Also large varicose veins and chronic venous insufficiency associated with dilated veins are associated with an increase in thrombotic events in subjects travelling for hours (8–12). The prevalence of DVT and SVT is generally higher in high-risk subjects and proportional to the length of the immobility period. Measures to prevent DVT and SVT include advice to passengers to exercise (standing, stretching, exercising, drinking water, avoiding constrictive clothes). Subjects with very relevant risk factors for DVT, such as, history of DVT, hormonal treatment, malignancy, recent surgery, should discuss additional, protective measures with their doctors including avoiding flights (13–19). Studied, effective preventive

Address correspondence and reprint requests to G. Belcaro, PhD, C.so Umberto I, 18, 65120 San Valentino, Pe, Italy; e-mail: cardres@pe.abol.it.

measures also include elastic stockings and antithrombotic prophylaxis with low-molecular-weight heparin (LMWH) (14–19).

In the LONFLIT studies (14–19) the incidence of DVT in high-risk subjects was greater than 4%. The LONFLIT 2 study—a prospective evaluation of DVT prevention with stockings (14,15)—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 (16–18).

The aim of this independent study was to evaluate the preventive effects of Pycnogenol®, a natural extract controlling permeability of capillary walls, preventing edema, inhibiting platelet aggregation, and improving microcirculation (20–23) in long flights (between 7 and 12 hours) in subjects at moderate to high-risk for DVT and for superficial thrombosis.

PATIENTS AND METHODS

The aim of the study was to evaluate subjects at moderate-to-high risk for DVT or SVT. Subjects were contacted before the flights (through the travel agents) and pre-included. A number of subjects (n = 76) were excluded on the basis of several considerations—compulsory use of anticoagulant or anti-thrombotic drugs (20 subjects), cardiovascular treatments (n = 38), possible low compliance (n = 18). We included 224 subjects (114 controls group and 110 in the treatment group). The subjects were randomly subdivided into two groups to evaluate prophylaxis with Pycnogenol in comparison with comparable placebo in 7- to 12-hour flights.

High-risk criteria for DVT are those previously indicated in LONFLIT studies 1, 2, and 3 (14–20) 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- to 13-MHz, high-resolution, linear probe (Sonosite, Bothell, WA) were used to study the venous system by compression of the major veins (femorals, popliteals, and tibials) (20,21).

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

Scanning Plan

Scanning was performed within 90 minutes before the flight and just after the flights (within 120 minutes). The event was defined as thrombotic when a non-compressible clot was observed by ultrasound (both in the deep vein system and in the superficial veins). The presence of inflammation of a superficial vein, without thrombosis, was defined phlebitis.

This study was not sponsored by the companies producing the materials quoted in this article. The compound was supplied—without conditions—by Horphag Research Management SA, Geneva, Switzerland.

Exercise Plan

An exercise plan was presented to all included subjects in an educational video explaining venous thrombosis and its prevention. It consisted of mild exercise (standing and moving legs for 5–10 minutes every hour), avoiding baggage between seats, and drinking regularly (100–150 mL of water every hour).

Pycnogenol Administration

Subjects received two capsules between 2 and 3 hours before flights with 250 mL of water and two capsules 6 hours later with 250 mL of water and one capsule the next day. Placebo and verum were packed in plastic bottles containing 10 capsules with instructions concerning how and when to take the capsules. Placebo capsules were administered accordingly to the control group with the same amount of fluid. The Pycnogenol capsules contained 100 mg of Pycnogenol (20–23).

Pycnogenol has been demonstrated to reverse symptoms of venous insufficiency as swelling, itching, and cramps. Pycnogenol only rarely may produce minor side effects.

The study hypothesis was that Pycnogenol reduces edema and symptoms, and may prevent DVT—which may be associated to the formation of edema in long flights. Also this compound controls the enhanced platelet aggregations in situations of immobility, particularly in moderate-to-high risk individuals.

Pycnogenol is a water soluble, dry extract from the bark of the French maritime pine. It is a

TABLE 1. Results

	Control	Pycno	Total	p
Included	105	106	211	ns
Completing the study	97	101	198	ns
Lost	8	5	13	ns
DVT	1	0	1	
SVT	4	0	4	<0.05
Events (%)	5.15	0	2.02	<0.025
ITT (failures)	13/105	4/106	17/211	<0.05
%	12.4	4.7	8.05	<0.05

The thrombotic events and drop-outs (subjects lost after the flight) are indicated. There was one limited (<3 cm in length), non-thrombotic (compressible) phlebitis in a varicose vein in one patient in the treatment group.

DVT, deep venous thrombosis; SVT, superficial venous thrombosis; Pycno, Pycnogenol; ITT, intention-to-treat analysis.

natural blend of constant proportions of bioflavonoids including catechin, epicatechin, taxifolin, oligomeric protocyanidins, and phenolic acids (ferulic acid and caffeic acid). Clinical studies in thousand of patients have shown in rare cases mild side effects such as gastrointestinal upset at the reccommended dosages (20).

Target of the study was the reduction thrombotic events—such as DVT or SVT. Tolerability and compliance were evaluated without a questionnaire, by direct questioning. The items concerning tolerability were structured in four items: gastrointestinal problems, skin alterations, signs of allergic reaction and any other manifestation. The problems were discussed informally with the subjects collecting unstructured, spontaneous reports, and observations.

Statistical analysis was conducted using non parametric tests and the analysis of variance considering event-free subjects completing the protocol. The specific incidence of thrombotic events (DVT, superficial thrombosis) was calculated and compared considering individuals and using intention-to-treat analysis.

RESULTS

Of the 244 pre-selected subjects 211 were actually included (33 excluded for several, nonmedical reasons) and 198 completed the study (13 were lost at the end of the flight for nonmedical problems; i.e., for difficult connections) (Table 1). The flight duration was on average 8 hours and 15 minutes (SD, 55 minutes) (range, 7.45–12.33 hours).

All subjects were scanned within 90 minutes before the flight and within 2 hours after disembarking. In the control group, there were five thrombotic events (one DVT and four superficial thromboses).

In the treatment group no thrombosis occurred. In one passenger a superficial phlebitis without thrombosis was observed. The varicose vein was inflamed, at the level of the internal part of the leg, distally to the knee, for a length of 2.5 cm, but no thrombus was visible by ultrasound in the vein lumen.

In the control group, all SVTs were associated to presence of clots and visible inflammation. The intention-to-treat analysis detects 13 failures in the control group (eight lost to follow up and five thrombotic events) out of 105 subjects (12.4%) vs. five failures (all lost) in the treatment group ($p<0.05$). In total there were 17 failures out of 211 included subjects (8.5%).

Side Effects, Tolerability

The tolerability was very good and there were no complaints or side effects. No subjects stopped the prophylaxis plan.

Signs/Symptoms

DVTs were all totally asymptomatic while all SVTs were associated to some degree of local pain and inflammation.

Ultrasound revealed the presence of limited (< 4 cm in length) but evident thrombosis in all the superficial veins involved in the control group.

CONCLUSIONS

Travel-related DVT and SVT are completely preventable conditions (1-9). Most flight or travel-related DVTs are neglected, being mostly asymptomatic (22–25). In long flights (> 12–18 hours) between 4% and 10% of passengers may be affected by DVT according to risk categories. New studies are still needed to evaluate the incidence and epidemiology of travel and flight-related DVT and the costs and benefits of different methods of prophylaxis (26–29). The evaluation of pulmonary embolism requires a large study population and more prolonged observations.

In long-haul flights, the real target is to prevent DVT. The main causes of the problem—immobility or reduced mobility, leg bending and limb swelling associated with the limited space available in flights on most aircrafts are associated to increased thrombogenicity of the blood, particularly at the level of the lower limbs.

An exercise plan is helpful but often it is not easy or sufficient. Controlling edema could be an important step to decrease the associated incidence of DVT. DVT in long-haul flights is an important safety issue. The incidence of DVT in high-risk subjects may be high and therefore prophylaxis is advisable. Exercise during flights, fluid intake, diet suggestions, less baggage on board to keep free leg space and larger empty spaces on planes may help, as well as suggestions from physicians not to travel in conditions of particularly high risk.

Varicose veins present a particular challenge. They are very common (23–28% of subjects in the population flying long-haul may have varices). They may thrombose and cause superficial thrombosis and phlebitis. Anti-thrombotic prophylaxis with Pycnogenol may offer a very important option for prophylaxis because it combines the effect of edema reduction and inhibition of platelet aggregation, which leads finally to less thrombotic events.

New observations (30–36) define better that the risk of flight-DVT is not minimal. Recent studies indicate new possibilities of prevention (41–43). New studies are very important, particularly to better define risks. Specific guidelines on this subject are not available at the moment. The observations resulting from this study indicate that flight-DVT prevention with Pycnogenol, particularly thrombotic events due to large varicose veins, is effective in moderate-to-high risk subjects.

REFERENCES

1. Geroulakos G, Hossain J, Tran T. Economy-class syndrome presenting as phlegmasia caerulea dolens. *Eur J Vasc Endovasc Surg* 2000;20:102.
2. Perry K. Blood clot kills woman after flight. *Guardian* 2001;23 Oct.
3. Homans J. Thrombosis of the deep leg veins due to prolonged sitting. *N Engl J Med* 1954;250:148.
4. Symington IS, Stack BHR. Pulmonary thromboembolism after travel. *Br J Chest* 1977;17:138.
5. Simpson K. Shelter deaths from pulmonary embolism. *Lancet* 1940;11:744.
6. Ferrari E, Chevallier T, Chapelier A, et al. Travel as a risk factor for venous thromboembolic disease: A case control study. *Chest* 1999;115:440.
7. Cruickshank JM, Gorlin R, Jennett B. Air travel and thrombotic episodes: The economy class syndrome. *Lancet* 1988;2:497.
8. Kraaijenhagen R, Haverkamp D, Koopman MMW, et al. Travel and risk of venous thrombosis. *Lancet* 2000;356: 1492.
9. Sarvesvaran R. Sudden natural deaths associated with commercial air travel. *Med Sci Law* 1986;26:35.
10. Landgraf H, Vanselow B, Schulte-Huerman D, et al. Economy class syndrome: Rheology fluid balance and lower leg oedema during a simulated 12-hour long-distance flight. *Aviat Space Envir Med* 1994;65:930.
11. AMA Commission on Emergency Services. Medical aspects of transportation aboard commercial aircraft. *JAMA* 1982;247:1007.
12. Gertler JP, Perry L, L'Italien G, et al. Ambient oxygen tension modulates endothelial fibrinolysis. *J Vasc Surg* 1993;18:939.
13. Bendz B, Rostrup M, Sevre K, et al. Association between acute hypobaric hypoxia and activation of coagulation in human beings. *Lancet* 2000;356:1657.
14. Belcaro G, Geroulakos G, Nicolaides AN, et al. Maladie veineuse thrombo-embolique apres vol aerien. Les etudes LONFLIT. *Angeiologie* 2001;53:17.
15. Belcaro G, Geroulakos G, Nicolaides AN, et al. Venous thromboembolism from air travel. The Lonflit Study. *Angiology* 2001;52:369.
16. Cesarone MR, Belcaro G, Nicolaides AN, et al. Venous thromboembolism from air travel: The Lonflit3 study. Prevention with Aspirin vs low-molecular weight-heparin (LMWH) in high-risk subjects: A randomised trial. *Angiology* 2002;53:1.
17. Belcaro G. Venous thrombosis and air-travel: Prevention with aspirin or low-molecular-weight-heparin. *Circulation* 2001(Suppl II)104:II-528.

18. Belcaro G, Geroulakos G, Nicolaides AN, et al. Prevention of deep venous thrombosis on long-haul flights. *J Am Coll Cardiol* 2002;39(Suppl 5):212A.

19. Anonymous. Stockings, heparin found to eliminate "coach class" syndrome. American Heart Association Scientific Sessions 2001, Nov 14; 3; p 8.

20. Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. *Int J Clin Pharmacol Ther* 2002;40,4:158.

21. Petrassi C, Mastromarino A, Spartera C. Pycnogenol® in chronic venous insufficiency. *Phytomedicine* 2000;7(5): 383.

22. Putter M, Grotemeyer KHM, Wurthwein G, et al. Inhibition of smoking-induced platelet aggregation by aspirin and Pycnogenol. *Thromb Res* 1999;95:155.

23. Schmidtke I, Schoop W. Le pycnogénol: Thérapeutique médicamenteuse de l'œdème statique. J *Suisse Médecine Glob* 1995;3/95:114.

24. Belcaro G, Nicolaides AN, Veller M. Venous Disorders: A Manual of Diagnosis and Treatment. Cambridge, MA: Saunders, 1996.

25. Belcaro G, Nicolaides AN. Noninvasive Investigations in Vascular Disease. London: Imperial College Press, 2001.

26. Belcaro G, Nicolaides AN, Stansby G. The Venous Clinic. Imperial College Press, London, 1999.

27. Cesarone MR, Meli E. Volare con Sicurezza. Jet-leg. Il problema dell'edema e della trombosi in voli di lunga durata. *Ediz Minerva Medica*, Turin 2001.

28. Thulesius O. Chronic venous insufficiency and varicose veins physiopathological sight points. *Lakartidningen* 1983;80(17):1791.

29. Cesarone MR, Belcaro G, Nicolaides AN, et al. The edema tester in the evaluation of swollen limbs in venous and lymphatic disease. *Panmin Med* 1999;41:10.

30. Belcaro G, Bollinger A, Hoffman U, Nicolaides AN (eds). *Laser-Doppler*. London: Med-Orion, 1995.

31. Nicolaides AN. Investigation of chronic venous insufficiency: A consensus statement. *Circulation* 2000;102:126.

32. Dalen JE, Hirsh J, Guyatt GH. Sixth ACCP Consensus Conference on Antithrombotic Therapy. *Chest* 2001; 119:1(Suppl).

33. *Prevention of Venous Thromboembolism*. International Consensus Statement. Edition 2002. London: Med-Orion, 2002.

34. Mendis S, Yach D, Alwan A. Air travel and venous thromboembolism. *Bull WHO* 2002;80:403.

35. Belcaro G, Cesarone MR, Shah S, et al. Prevention of edema, flight microangiopathy and venous thrombosis in long flights with elastic stockings. A randomized trial: The LONFLIT 4 Concorde Edema-SSL Study. *Angiology* 2002;53(6):635.

36. Cesarone MR, Belcaro G, Errichi BM, et al. The LONFLIT4—Concorde Deep Venous Thrombosis and Edema Study: Prevention with travel stockings. *Angiology* 2003; 54(2):143.

37. Rosendaal FR, Buller HR, Kesteven P, Toff WD. Long haul flights and deep vein thrombosis: Who is at risk? *Br J Haematol* 2003;120(2):367.

38. Campbell C, Rayner CF. Guidelines on prevention of venous thromboembolism during long haul flights. *Thorax* 2003;58(1):91.

39. Schwarz T, Langenberg K, Oettler W, et al. Deep vein and isolated calf muscle vein thrombosis following long-haul flights: Pilot study. *Blood Coagul Fibrinolysis* 2002; 13(8):755.

40. Arya R, Barnes JA, Hossain U, et al. Long-haul flights and deep vein thrombosis: A significant risk only when additional factors are also present. *Br J Haematol* 2002;116(3):653.

41. Murphy JF. The folded deckchair position: The problem of long-haul flights. *Ir Med J* 2001;94(9):260.

42. Hosoi Y, Geroulakos G, Belcaro G, Sutton S. Characteristics of deep vein thrombosis associated with prolonged travel. *Eur J Vasc Endovasc Surg* 2002;24:235.

43. Cesarone MR, Belcaro G, Di Renzo A, et al. The pilgrim syndrome. Epidemiology and investigations of long-travel pilgrimage-related thrombosis. *Eur Venous Forum Web J* 2003;1:1.