Air travel and the risk of venous thromboembolism

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Abstract

Passenger air travel is a convenient and frequently used mode of transportation across the globe. However, certain health risks are associated with commercial flights, many of which are inherent to this distinctive method of transportation. It has been shown that air travel innately carries an increased risk of the development of venous thromboembolism (VTE), and although small, this risk is significantly higher than in the general, healthy, non-flying population. Individual air travellers are strongly encouraged to consult a suitable healthcare professional for an individual risk assessment and guidance on suitable or required prophylactic measures prior to undertaking either frequent or long-distance travel via aeroplane.

Keywords: air travel, long-haul flight, DVT, pulmonary embolism, venous thromboembolism, VTE

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Introduction

Millions of passengers traverse the skies annually by making use of the benefits and convenience of domestic and international air travel. However, certain health risks are associated with commercial flights, many of which are inherent to this distinctive mode of transportation. These include medical issues such as hypobaric hypoxia, cosmic radiation exposure and jet lag.[1,2]

This article will focus on the life-altering and potentially life-threatening[1,2] risk of suffering an acute episode of venous thromboembolism (VTE), with particular regard to passenger air travel.

General considerations

It has been shown that a definite association exists between long-haul flights, especially when they are more than eight hours in duration, and VTE. Interestingly enough, the risk for business class travellers is similar to that of travellers in the economy class cabin. However, it is greater for passengers who occupy the non-aisle seats. This is because 75% of air travel-associated episodes of VTE have been linked to immobility during long-distance flights.[3-5]

The risk of VTE is increased with long-haul flights, especially those over eight hours, and is higher for passengers with pre-existing risk factors such as obesity, recent surgery, or genetic predispositions[3-5]

Conversely, the overall risk of developing air travel-related VTE remains very low, but it has still been shown to be significantly higher than that associated with the healthy, non-flying population. It can be said that an average long-haul flight of 12 hours in duration, with 400 passengers on board, will result in a 0.2% incidence rate of symptomatic VTE[3-5] (Figure 1).

Definition of venous thromboembolism

VTE refers to the combination of deep vein thrombosis (DVT) and pulmonary embolism (PE). The underlying pathophysiological process seems to involve venous stasis, with resultant coagulation and thrombus formation. Should a venous thrombus, or a portion of it, become dislodged from a vessel wall in the lower extremity, for example, the resultant embolus will travel through the venous blood circulation to reach the inferior vena cava, the right atrium and right ventricle, the pulmonary artery, and will ultimately become lodged in one of the smaller arteries of the lung, resulting in PE.[2,3]

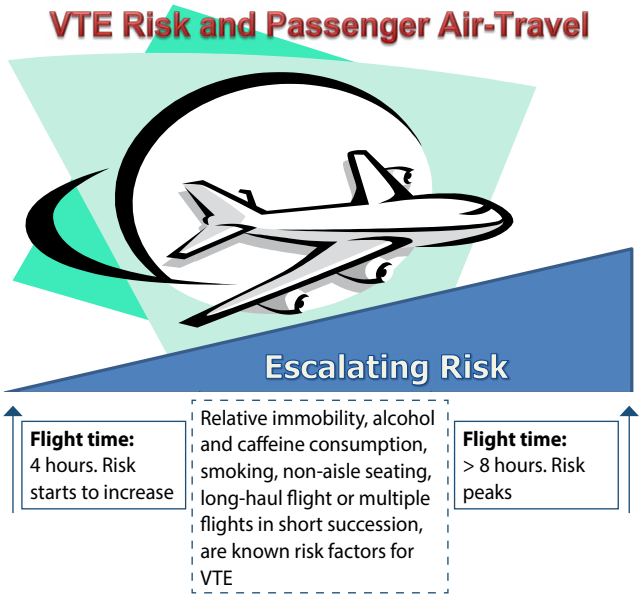

Figure 1: The risk of thromboembolism associated with passenger air travel[1-5]

VTE: venous thromboembolism

As the name implies, the deep veins of the lower extremities constitute the most common sites of DVT. There is a significant risk of acute PE secondary to such venous thrombi, i.e. approximately 50% in the case of DVT in the proximal lower extremity, and roughly 25% in the case of the distal lower extremities.[2-5] Severe PE may prove to be fatal. However, a DVT could develop in the upper extremity as well.

Risk factors for venous thromboembolism, including those that relate to air travel

Generally, the risk factors that are associated with VTE may be classified as either inherited (genetic) or acquired (environmental). The majority of VTE-associated events are linked to a combination of the two. It should also be noted that these risk factors have an additive effect on an individual's propensity for developing VTE.

Various genetic factors may predispose a person to a state of so-called hypercoagulability, and include the following:[3]

- Clotting factor V Leiden mutation, a prothrombin gene mutation (G20210A), or elevated levels of clotting factor VIII (the latter could also be an acquired condition)
- An inherited deficiency of protein C or S, or of antithrombin, a naturally-occurring "anticoagulant"
- Hyperhomocysteinemia

Of the list of acquired risk factors, the following are especially important in the community (i.e. including regular air travellers) setting:[2,3,4,5]

Age and gender-related risk factors

Age and gender-related risk factors include:

- Advancing age, from 40 years onwards
- Women's health-related risks, which include the use of oral contraceptives and hormone-replacement therapy, as well as hypercoagulability of pregnancy and the puerperium
- The male gender
- Frailty and immobility

Associated risk factors with medical illness

Associated risk factors with medical illness include:

- "Lifestyle diseases", such as hypertension, diabetes mellitus and dyslipidemia
- Strokes with paralysis or paresis, acute medical illness (including chronic obstructive pulmonary disease, congestive cardiac failure and pneumonia), antiphospholipid syndrome, nephrotic syndrome and inflammatory bowel disease
- Patients with cardiac pacemakers
- Ambulatory patients with indwelling central venous catheters
- Active cancer and certain cancer chemotherapeutic agents
- Varicose veins and prior episodes of VTE
- Conditions that result in venous insufficiency

Surgical risk factors

Surgical risk factors include:

- Recent trauma resulting in compression of the veins or immobilisation, including plaster cast immobilisation
- Major surgery, especially the larger orthopaedic procedures, such as hip and knee replacement surgery, and the surgical repair of hip fractures

Lifestyle-related risk factors

Lifestyle-related risk factors include:

- Smoking
- Obesity, especially when the body mass index exceeds 30 kg/m^2
- Conditions or circumstances that may result in prolonged immobility and venous stasis, such as long-distance travel, especially air travel, or being bedridden for more than three consecutive days

Additional risk factors for air travellers

Two major risk factors to consider are flight duration and the person's height. Long-haul flights carry a greater risk owing to increased periods of immobility, especially single long-haul flights that last 8-10 hours or more. However, multiple long-haul flights of at least four hours in duration, or frequent flights of any duration which occur in short succession of one another, also carry an increased risk for VTE. In terms of body height, persons who are at an increased risk are those who are shorter than 1.65 m, or taller than 1.85 m in height.[2]

Furthermore, risk factors such as prolonged immobility, which is especially associated with long-haul flights, and with passengers in the non-aisle seats in particular, together with dehydration (with a resultant increase in blood viscosity) and hypobaric hypoxia (due to the pressurised passenger cabin), all increase the risk of VTE associated with air travel in patients who already have one or more of the underlying risk factors for VTE prior to their flight.[1]

Venous thromboembolism prophylaxis for air travellers

VTE that is associated with passenger air travel is an emerging public health concern, but there still seems to be a lack of sufficient evidence in terms of both definite causality and effective prophylactic measures. Yet, a few basic principles, based on current knowledge in this field, may be proposed for the prevention of VTE during air travel, as illustrated in Figure 2.[1,2]

Current recommendations for prevention measures include frequent ambulation, calf muscle exercises, sitting in aisle seats when possible, and the use of compression stockings for those at high risk[4,5]

Anticoagulant prophylaxis

A specific subset of passengers who find themselves at a significantly higher risk of developing acute, air travel-related VTE will require pharmacological intervention in the form of

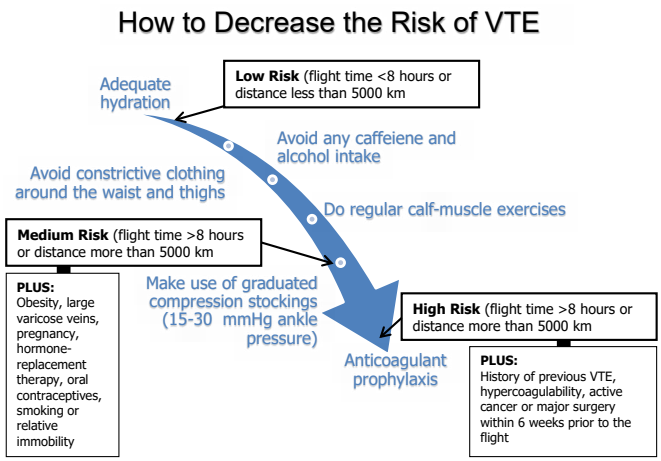

Figure 2: Measures to decrease the risk of air travel-related thromboembolism. Note that these measures are additive, relative to the degree of risk, and should be based on an individual risk assessment[1]

VTE: venous thromboembolism

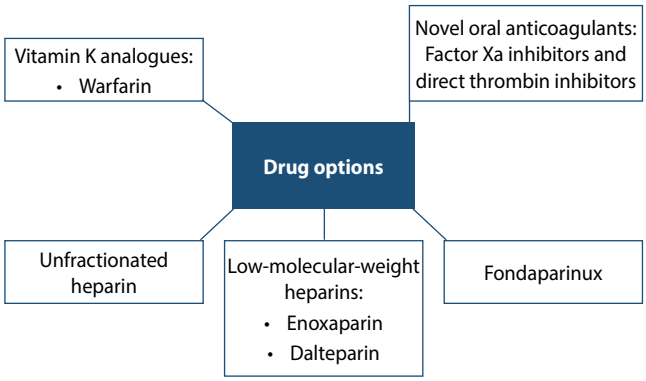

Figure 3: Possible venous thromboembolism prophylaxis drug options

anticoagulant prophylaxis. Figure 3 illustrates the various options that are currently available.

The drugs that are used to prevent VTE and emboli of cardiac origin, as seen in patients with atrial fibrillation for example, are heparin (unfractionated or standard heparin and the newer forms of heparin with low molecular weight, such as enoxaparin and dalteparin), factor Xa inhibitors, and warfarin, a vitamin K antagonist. Apixaban, a direct factor Xa inhibitor, has been extensively studied for its efficacy and safety in preventing VTE. In the context of air travel, while specific studies on apixaban are limited, its pharmacological profile suggests potential benefits. Apixaban has been shown to be effective in reducing the risk of VTE in various clinical settings, such as in patients with atrial fibrillation or those undergoing major orthopaedic surgery. Its oral administration and predictable pharmacokinetics make it a convenient option for travellers. However, its use specifically for air travel-related VTE prevention requires further investigation to establish clear guidelines.[6,7,8] Warfarin inhibits the hepatic synthesis of clotting factors that depend on vitamin K, namely factor II (prothrombin), VII, IX and X (as well as protein C and S). This drug is renowned for its long list of potential drug interactions and variations in individual responses to this drug may be substantial.

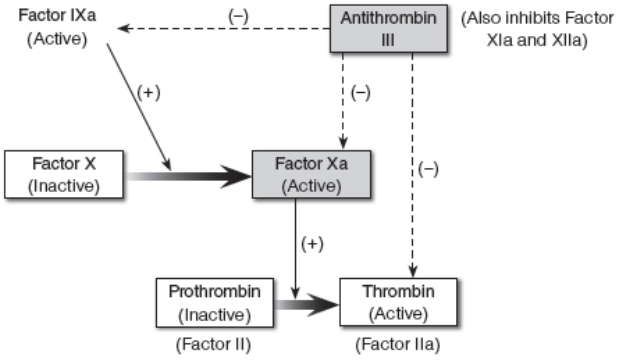

Figure 4: The relationship between factor Xa, thrombin and antithrombin III[5]

Careful monitoring and good compliance are essential for the success of anticoagulant therapy with warfarin.[3,5]

Low-molecular-weight heparins (LMWHs) are fractions of standard heparin and are becoming increasingly more popular than the unfractionated form. Heparin enhances the action of antithrombin III. The two clotting factors that are the most sensitive to the anticoagulant effects of unfractionated heparin (UFH) are factor IIa (thrombin) and Xa, while LMWHs favour factor Xa. Fondaparinux is a synthetic agent that specifically inhibits factor Xa, i.e. the activated form of clotting factor X. The heparins and fondaparinux are indirect thrombin-inhibitors (Figure 4).[3,5]

Patients who receive anticoagulants should be monitored for signs of spontaneous bleeding, including microscopic and macroscopic haematuria, bleeding gums and nosebleeds.

Current recommendations mainly focus on the LMWHs, and the factor Xa inhibitor, fondaparinux.

Low-molecular-weight heparins

LMWHs are obtained from UFH through chemical depolymerisation. The preparation of LMWHs occur through different methods of depolymerisation. To some degree, these varying methods of preparation result in differences in their pharmacokinetic properties and anticoagulant profiles, such that these drugs are not clinically interchangeable.[9] Enoxaparin and dalteparin are the LMWHs of choice for the prophylaxis of VTE during air travel.[2]

Mechanism of action

LMWHs mainly act on coagulation factor Xa, and also, but to a lesser extent, on thrombin (factor IIa). Positioned at the junction of the intrinsic and extrinsic coagulation pathways, factor Xa transforms prothrombin into thrombin. Enoxaparin exerts its effect on this crucial coagulation factor (Xa), which inhibits the successive step in the cascade, the generation of thrombin. Enoxaparin also acts on thrombin, which is essential for the formation of fibrin, a necessary component of blood clots. The added thrombin activity of enoxaparin restricts the intensification of the coagulation cascade by thrombin.[10-14]

Recommended dosage

The recommended dosage is as follows:

- *Enoxaparin sodium:* 40 mg subcutaneously as a single injection just before departure
- *Dalteparin:* 5 000 IU subcutaneously prior to departure[2]

Drug interactions

On every occasion possible, agents which may increase the risk of haemorrhage should be discontinued prior to initiation of LMWH therapy. These agents include medication such as other anticoagulants and platelet inhibitors (including acetylsalicylic acid, salicylates, nonsterioidal anti-inflammatory drugs, dipyridamole or clopidogrel). If co-administration is necessary, close clinical and laboratory monitoring will need to be conducted.[11] Furthermore, it should be noted that aspirin alone is of limited value in this setting. Therefore, it is not recommended for the prevention of air travel-related VTE.[1]

Factor Xa inhibitors

Fondaparinux is an indirect factor Xa inhibitor.[12,16]

Mechanism of action

Fondaparinux is classified as a synthetic analogue of the antithrombin-binding pentasaccharide. This pentasaccharide is also present in UFH or in the LMWHs. Fondaparinux has a molecular weight, which is approximately three times lower than that of LMWHs.[12]

Fondaparinux sodium's antithrombotic activity is the end result of antithrombin III-mediated selective inhibition of factor Xa. The selective binding of fondaparinux to antithrombin III, enhances (approximately 300 times) the natural neutralisation of factor Xa by antithrombin III. Neutralisation of factor Xa disrupts the blood coagulation cascade which inhibits thrombin formation and thrombus development.[13]

Fondaparinux sodium lacks the ability to inactivate thrombin (activated factor II), and has no known effect on platelet function. At recommended dosages, fondaparinux sodium does not prolong prothrombin time and has a very weak effect on activated partial thromboplastin time.[12]

Recommended dosage

It is recommended that a single dosage of 2.5 mg is administered subcutaneously prior to departure.[2]

Drug interactions

Discontinuation of agents that may enhance the risk of haemorrhage prior to initiation of therapy with fondaparinux is recommended unless essential. If co-administration is a must, patients should be monitored closely for haemorrhage.[13]

Adverse effects

The most common adverse effects associated with the use of fondaparinux are bleeding complications and mild local irritation, following subcutaneous injection.[13]

Other potential options

Other potential options include rivaroxaban, dabigatran, apixaban, and other newer oral anticoagulants that are still in clinical development. Their use in the setting of VTE prevention with regard to air travel still needs to be elucidated:

- *Rivaroxaban:* Rivaroxaban is a highly selective, direct factor Xa inhibitor.[17] It is an orally-bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa, and does not require the presence of a co-factor, such as antithrombin III, for its activity. The activation of factor X to factor Xa through the intrinsic and extrinsic pathways plays an essential role in the cascade of blood coagulation.[14]
- *Dabigatran:* Dabigatran is an oral, reversible, direct thrombin inhibitor.[18] Dabigatran and its active metabolites are competitive, direct thrombin inhibitors. Since thrombin assists with the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombi. Both free and clot-bound thrombin and thrombin-induced platelet aggregation are inhibited.[15]

Conclusion

It has been shown that air travel inherently carries an increased risk of the development of VTE, and although small, this risk is significantly higher than that in the general, healthy, non-flying population. Individual air travellers are strongly encouraged to consult a suitable healthcare professional prior to undertaking either frequent or long-distance travel via aeroplane for an individual risk assessment and guidance on suitable or required prophylactic measures.

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