Review Article

# Prevention of Deep Vein Thrombosis and Pulmonary Embolism in the Perioperative period: a Review

Aliya Ahmed
Department of Anaesthesia, Aga Khan University Hospital, Karachi.

## Introduction

The term thrombosis refers to the formation of a clot [thrombus] inside a blood vessel and an embolus is a fragment of the thrombus that breaks off and travels in the blood until it settles at a sight of vascular narrowing. Deep vein thrombosis (DVT), usually involving a leg vein, and pulmonary embolism (PE) are the manifestations of the same disease entity and can be collectively referred to as venous thromboembolism (VTE).[1] VTE is an important cause of perioperative morbidity and mortality.[1-3] Atleast 30 cases of DVT identifiable by phlebography can be expected among 100 patients who have undergone general surgical operations of moderate severity if they are not given perioperative antithrombotic prophylaxis.[2]

As there is a scarcity of reliable autopsy data, it is not clear how often fatal PE occurs after surgery. The risk varies with the surgical procedure and PE may account for 10% of all postoperative deaths following hip arthroplasty and fatal PE accounts for 3-4% of all symptomatic VTE events.[1] A thorough preoperative assessment and preparation before major surgery must include the issue of the prevention of DVT and PE in the perioperative period in an attempt to decrease the incidence of this potentially fatal perioperative complication. Correct choice of the thromboprophylactic regime for each patient and initiating it at the right time is important to decrease the incidence of perioperative VTE.

Selection of the appropriate prophylactic regime and providing it for the appropriate duration in the perioperative period depends not only upon the knowledge of the various modalities available for the prevention of VTE but also upon the awareness of the gravity of this complication, among both the surgeons and the anaesthesiologists. This article will review the etiology and risk factors of perioperative DVT and PE and the various pharmacological and non-pharmacological modalities available for its prevention. The term VTE will be used when referring to DVT and PE together.

### Etiology and risk factors

The etiological factors for DVT include venous stasis (reduced blood flow), a hypercoagulable state (potential for abnormal clot formation) and the presence of vessel injury (loss of vascular integrity).[3] These three factors are called the Virchow's triad and are common findings in the postoperative period especially after major surgery. The risk of symptomatic thromboembolism depends to a large extent upon the type and duration of surgery, presence of other risk factors (Table 1), duration and extent of postoperative immobilization and use or not of thromboprophylactic measures.[4]

Age, co-morbids and type of anaesthesia (general or regional) also contribute to the incidence rate and should be considered when assessing a patient's risk for postoperative DVT.[3] The incidence of asymptomatic VTE, which is considerably higher than that of symptomatic VTE, has been reported to be 20-25% after general surgery and 45-60% after orthopaedic surgery involving the hip or knee. Results of one study[5] showed that neurosurgery involving entry into brain or meninges and orthopaedic surgery involving the hip was associated with the highest incidence of symptomatic thromboembolism. Other procedures found to be associated with a higher risk in that study included major vascular surgery, small or large bowel resection, radical cystectomy, gastric bypass for obesity and renal transplantation. Operations associated with a low risk include laparoscopic cholecystectomy, appendectomy, inguinal hernia repair, transurethral resection of prostate, and radical neck dissection.[4]

The incidence of postoperative VTE is low in patients younger than 40 years and increases with age.[6] Prolonged immobilization due to any reason including stroke, surgery, trauma, and obesity leads to an increased risk of developing postoperative DVT mainly due to venous stasis.[7] Medical conditions like congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) are associated with a higher incidence of VTE.[8] Cancer is an important risk factor for postoperative VTE. The reason for this could be that neoplastic cells generate thrombin and synthesize various procoagulants.[9] Oral contraceptives containing estrogen and hormone-replacement therapy increase the risk of VTE especially at the start of therapy.[10]

Patients who receive epidural or spinal anaesthesia have a more than 50% decreased incidence of postoperative VTE after total hip or knee replacement compared to those having these surgeries under general anaesthesia.[1,11] However, the long-term outcome is not affected by the anaesthetic technique.[12]

**Table 1. Risk factors for postoperative thromboembolism.**

| |
|---|
| **Venous stasis** |
| Bed rest |
| Trauma |
| Recent surgery |
| Stroke |
| Venous insufficiency |
| Congestive heart failure |
| Pregnancy |
| Morbid obesity |
| History of venous stasis |
| **Hypercoagulability** |
| Estrogen oral contraceptives |
| Postoperative state |
| Deficiency of protein C or protein S |
| Antithrombin III resistance |
| Inflammatory bowel disease |
| Malignancy |
| Post trauma |
| **Abnormality of the vessel wall** |
| Trauma |
| Surgery |
| Varicose veins |
| Vasculitis |
| Drug induced irritation |

## Prevention of Venous Thromboembolism

A variety of non-pharmacological and pharmacological agents are available for the prophylaxis of VTE (Table 2).

**Table 2. Modalities for VTE Prophylaxis.**

| |
|---|
| **Non-Pharmacological Modalities** |
| Elastic compression stockings |
| Intermittent pneumatic compression devices |
| Early ambulation |
| Inferior vena cava filters |
| **Pharmacological Agents** |
| Low dose unfractionated heparin |
| Low molecular weight heparin |
| Warfarin (low dose / intermediate dose: INR 2.0-3.0) |
| Aspirin (usually as an adjunct) |
| Dextran (not popular currently) |

VTE: Venous thromboembolism.

The selection of the prophylactic regimen should be individualized for each patient depending upon the surgical procedure, individual patient risk factors and safety and efficacy of the thromboprophylactic agent. In this context the patients at low risk for VTE are those under 40 years of age having general surgical, urologic and gynaecological non-cancer surgeries of short duration (< 60 min).[2] Moderate risk includes patients less than 40 years with no added risk factors having major surgery or those between 40 and 60 years having no added risk factors for VTE undergoing minor surgery or patients less than 40 years but having risk factors for VTE, undergoing minor procedures (Table 3). High-risk patients are those over 60 years of age, having additional risk factors for VTE and undergoing minor surgical procedures or those over 40 years with no additional risk factors having major surgery. Patients at very high risk for VTE are those above 40 years with multiple VTE risk factors having major surgery (Table 3).[2,4]

**Table 3. Postoperative Venous Thromboembolism: Risk stratification.**

| Age (Years) | Presence of Risk Factors | Extent of Surgery | Degree of Risk |
|---|---|---|---|
| < 40 | No | Minor | Low |
| < 40 | No | Major | Moderate |
| 40-60 | No | Minor | Moderate |
| Any age | Yes | Minor | Moderate |
| > 60 | Yes | Minor | High |
| > 40 | ± | Major | High |
| < 40 | Yes | Major | High |
| > 40 | Multiple | Major | Very high |

The risk of thrombosis and bleeding should be weighed for each patient and the timing and dosage of the prophylactic agent adjusted accordingly. A description of the various non-pharmacological and pharmacological agents available for the prophylaxis of VTE follows.

## Non Pharmacologic Modalities

### Elastic Compression Stockings

Graduated-compression stockings can provide adequate prophylaxis in patients at low risk for DVT.[13] The stockings should be applied prior to surgery and continued until full ambulation.[3] They improve venous flow from the foot to the knee, but improperly fitting stockings will cause a reversed effect leading to more harm than benefit.[13] The main advantages of elastic compression stockings are that they are cheap, convenient, easy to use and properly fitting stockings, when applied correctly, have proven efficacy for patients at low risk for DVT.[2-4,13] Although they do not provide adequate prophylaxis when used alone in patients at moderate to high risk for perioperative VTE, they enhance the effect of other thromboprophylactic modalities[4], and should be used in all surgical patients at risk unless there is

Thus, properly fitting elastic stockings should be used as an adjunct to other thromboprophylactic modalities for moderate to high risk patients and may be used as a sole agent in patients at low risk.

**Intermittent Pneumatic Compression Devices**

These devices cause intermittent external compression of the legs and thighs with inflatable cuffs thereby pumping venous blood and reducing stasis. Intermittent pneumatic compression (IPC) devices are also said to aid the clearance of prothrombotic clotting factors and increase endogenous fibrinolysis by stimulating the vascular endothelial wall[14] although, more recently, another study has not found this increase in fibrinolysis with IPC devices.[15] Improper application of these devices could be a frequent reason for the failure of this form of prophylaxis against DVT[16], and probably for this reason this form of prophylaxis has not been found to be effective in obese patients.

In addition to the calf and thigh IPC devices, foot pumps are also available which compress the planter venous plexus, but they have not been studied extensively.[17] IPC devices are safe and are especially useful in patients who are at an increased risk of bleeding with anticoagulant therapy. For the same reason these devices are attractive for prophylaxis in patients who have undergone neurosurgical procedures.[18] These devices should be used in conjunction with pharmacological methods of VTE prevention in patients who are at a high risk of perioperative VTE but can be used as sole agents for those who are at a moderate risk, while in case of gynaecological surgery they can be used as sole agents even in high risk cancer patients.[19]

**Early Ambulation**

Early ambulation should be strongly encouraged in all post surgical patients. It has proved to be associated with a lower incidence of both symptomatic and ultrasonically diagnosed thromboembolism after hip surgery.[20] Early ambulation, in older persons is associated with fewer complications and shorter hospital stay and in low risk general, urologic and gynaecologic surgeries, early ambulation alongwith elastic stockings can be used for prophylaxis of VTE without the addition of pharmacologic prophylactic agents.[1]

**Inferior Vena Cava Filters**

Inferior vena cava (IVC) filters are meant to interrupt blood flow to prevent pulmonary embolization.[21] Their use is recommended when there is a failure of or contraindication to anticoagulation and when anticoagulation leads to serious hemorrhage and has to be discontinued. In the last situation an IVC filter should especially be considered for patients with recent VTE.[21] These filters are also appropriate for patients with VTE who have recurrent pulmonary embolism despite adequate anticoagulant therapy.[1] The complications of IVC filters include IVC thrombosis, filter migration, recurrent DVT and postphlebitic syndrome[21] which is a chronic complication of venous thrombosis that consists of pain, swelling and occasionally ulceration of the skin of legs. Thus, IVC filters should be used only when strongly indicated and temporary filters should be preferred.

**Pharmacological Thromboprophylaxis**

The most widely used agents for the prevention of perioperative VTE include unfractionated heparin (UH), low molecular weight heparin (LMWH), warfarin and antiplatelet agents. This article will briefly review these agents. These agents differ in their efficacy and in the seriousness of their main side effect, that is, bleeding. The choice of the antithrombotic agent should be individualized depending upon the presence of risk factors, the type of surgery and the risk of hemorrhagic complications.

**Unfractionated Heparin**

Small subcutaneous doses of heparin given in a dose of 5000 IU two or three times daily have shown to be effective in decreasing the incidence of fatal postoperative PE in patients at a moderate risk of VTE.[22] The first dose can be given two hours preoperatively but should be started earlier in admitted patients who are confined to bed. Postoperative initiation of UH has also been shown to be effective.[23]

Low dose UH (5000 IU 8-12 hourly subcutaneously) is a useful prophylactic agent for most general surgical, gynaecologic and urologic surgical patients and non-pharmacological modalities like elastic stockings and IPC devices may be added in higher-risk patients.[3,22] Low dose UH is less effective compared with LMWH in very high risk neurosurgeries and orthopaedic surgeries.[24] It is therefore not the prophylactic agent of choice for very high risk procedures. Its main side effects include bleeding and heparin induced thrombocytopenia [HIT]. Haemorrhagic complication and serious bleeding is rare as long as there is no other haemorrhagic diathesis.[22] HIT associated with UH has been shown to have a strong association with postoperative VTE.[25]

**Low Molecular Weight Heparin**

The common LMWH preparations include enoxaparin, dalteparin, rogiparin and tinzaparin. Enoxaparin (claxane) and dalteparin (fragmin) are currently available in Pakistan. LMWH exerts its effect by the inhibition of factor Xa mediated by antithrombin. There is evidence that the incidence of bleeding with LMWH is lower compared with low dose UH and the efficacy has been found to be equivalent.[24] This makes LMWH more attractive in many surgical patients. A longer biological half life and predictable plasma concentration of LMWH allow

it to be administered once or twice daily in a fixed dose without the need for laboratory tests.[26] This enables outpatient management when extended DVT prophylaxis is required, thus reducing inpatient costs. The usual dosage is enoxaparin 30mg subcutaneously (s/c) 12 hourly or 40mg s/c once daily or dalteparin 2500-5000 IU daily s/c.

There have been some unfavorable reports of the use of LMWH for thromboprophylaxis. In one report an unexpectedly high rate of DVT followed abdominal surgery despite daily doses of LMWH at recommended levels.[27] No clear reasons for the increased rate of DVT encountered in this study came forth and other workers did not obtain a similar result.[24,26] In elective surgery of hip and knee, a once daily dose of LMWH [Logiparin] was associated with a higher incidence of serious bleeding complications when compared to warfarin prophylaxis with an INR of 2.0 to 3.0, although LMWH was found to be more effective.[28] However, the overall review of LMWH[2-4,24,26] suggests that it is an effective and safe agent that can be used on an outpatient basis.

**Warfarin**

Warfarin, a vitamin K antagonist, is a useful agent for VTE prophylaxis, especially in high risk patients.[29] It exerts its action by interfering with the carboxylation of coagulation factors II, VII, IX, X and proteins C and S.[3] The half life of these coagulation factors varies widely, from approximately 6 hours for factor VII to 50 hours for factor II. This is the reason for the long time required for return of normal coagulation following discontinuation of warfarin. Increased warfarin effect occurs in severe hepatic or renal insufficiency as well as with acute alcohol use, decreased dietary intake of vitamin K and decreased protein binding of warfarin.[3] The dose recommended for DVT prophylaxis is usually adequate to treat an established but undetected thrombosis.[2,4]

The prothrombin time and the International Normalized Ratio (INR) are used to monitor therapy with warfarin. The target range of INR for an individual patient is guided by the risk of thromboembolism and the nature of surgery. The target INR of 2.0 to 3.0 has been found to be effective.[29] The potential for bleeding complications is a concern and adequate monitoring is essential, but the incidence has not been found to be troublesome if the INR is kept between 2.0 to 3.0.[29] For the purpose of VTE prophylaxis warfarin use is indicated primarily for very high risk patients with lower limb orthopaedic surgery, neurosurgery or those with malignant lesions.[3] It is useful for patients who require extended thromboprophylaxis especially those undergoing total hip arthroplasty. It can be started either the night before surgery or immediately after surgery. It can also be started 10-14 days preoperatively to maintain an INR of about 1.5 and then increasing the dose postoperatively to achieve an INR of 2.5.[4,29] Elderly patients or those with low serum albumin levels require lower doses of warfarin.

**Antiplatelet Agents**

Aspirin has been studied as a prophylactic agent against DVT but its use for this purpose is controversial.[30] It is not recommended as a sole prophylactic agent for perioperative VTE prevention, but research has shown a role of aspirin for VTE prevention after hip fracture surgeries when used in combination with other thromboprophylactic agents.[31] It may also provide additional benefit to patients with cardiovascular disease. Patient's and physician's familiarity with aspirin makes it a useful agent to be prescribed at discharge for additional long term protection when indicated.

**Other Agents**

The dextrans are branched chain polysaccharides, which increase flow in the microcirculation[32] and have shown to prevent VTE. They have to be administered intravenously and can lead to allergic reactions including anaphylaxis. For this reasons they are not currently being used for VTE prophylaxis.

Hirudin is a constituent of leech saliva and has anticoagulant properties. Recombinant DNA techniques are being used to produce biologically active compounds related to hirudin. One of these agents, disirudin, has been compared with enoxaparin for VTE prophylaxis and has been found to be more effective with a similar safety profile.[33] These agents are potent inhibitors of thrombin and their action is independent of antithrombin III. Other agents are in different stages of development and require trials to prove their efficacy and safety.

**Timing and Duration Of Prophylaxis**

Optimal timing and duration of prophylaxis is important, especially in high risk patients. For total hip and knee replacements LMWH can be started the night before surgery followed by once daily injections.[34] In the United States the usual practice is to start LMWH postoperatively. Extending the prophylaxis for 4-6 weeks is recommended for total hip replacement[35] although this is associated with a modest increase in the risk of minor bleeding.

For patients having other elective surgical procedures, prophylaxis should be started preoperatively, that is, as soon as the risk of developing DVT begins, with an appropriate combination of non-pharmacological and pharmacological modalities, and continued during hospitalization.[2-4] Extended prophylaxis should be provided to patients at a higher risk of VTE. These include patients with active cancer, with history of VTE, patients who are obese or cannot ambulate for any reason. Either LMWH

(enoxaparin 40mg or dalteparin 5000 IU once daily s/c) or warfarin (to keep INR around 2.5) can be used for extended prophylaxis. Warfarin is cheaper as compared to LMWH but it requires laboratory monitoring for adequate anticoagulation and prevention of bleeding complications.

## Conclusion

Venous thromboembolism is a major preventable cause of postoperative morbidity and mortality. When prescribing thromboprophylaxis for any patient, proper risk stratification should be implemented so that the risk of bleeding and thromboembolism could be balanced. Local practice guidelines should be developed with a combined effort of the surgeons, the anaesthesiologists and the physicians, keeping in mind the availability and cost effectiveness of the various modalities described for thromboprophylaxis. Pharmacological and non-pharmacological modalities should be used in appropriate combinations to achieve effective thromboprophylaxis for each patient.

## Reference


1. Ginsberg JS. Management of venous thromboembolism. N Engl J Med 1996;335:1816-28.
2. Weinmann EE, Salzman EW. Deep-vein thrombosis. N Engl J Med 1994;331:1630-41.
3. Sitzman B.T. Prevention of perioperative deep venous thrombosis and pulmonary embolism. [online] 1998. Available from: www.dcmsonline.org/jax-medicine/1998journals/december98/ thrombosis.htm.
4. Kaboli P, Henderson MC, White RH. DVT prophylaxis and anticoagulation in the surgical patient. Med Clin N Am 2003;87:77-110.
5. White RH, Romano PS, Zhou H. A population-based comparison of the 3 month incidence of thromboembolism after major elective/urgent surgery. Thromb Haemost 2001;86, p. 2255. [PubMed]
6. Heit JA, Melton LJ 3rd, Lohse CM, Petterson TM, Silverstein MD, Mohr DN, et al. Incidence of venous thromboembolism in hospitalized patients vs community residents. Mayo Clin Proc 2001;76:1102-10.
7. Munin MC, Rudy TE, Glynn NW, Crossett LS, Rubash HE. Early inpatient rehabilitation after elective hip and knee arthroplasty. JAMA 1998;279:847-52.
8. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LT 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med 1999;159:445-53.
9. Piccioli A, Prandoni P, Ewenstein BM, Goldhaber SZ. Cancer and venous thromboembolism. Am Heart J 1996;132:850-5.
10. Vandenbroucke JP, Helmerhorst FM. Risk of venous thrombosis with hormone-replacement therapy. Lancet 1996;348:972.
11. Jorgensen LN, Rasmussen LS, Neilsen PT, Leffers A, Albrecht-Beste E. Antithrombotic efficacy of continuous extradural analgesia after knee replacement. Br J Anaesth 1990;66:8-12.
12. Davis FM, Woolner DF, Frampton C, Wilkinson A, Grant A, Harrison RT, et al. Prospective multicenter trial of mortality following general or spinal anaesthesia for hip fracture surgery in the elderly. Br J Anaesth 1987;59:1080-8.
13. Wells PS, Lensing AW, Hirsh J. Graduated compression stockings in the prevention of postoperative venous thromboembolism; a meta-analysis. Arch Intern Med 1994; 154:67-72.
14. Kessler CM, Hirsch DR, Jacobs H, MacDougall R, Goldhaber SZ. Intermittent pneumatic compression in chronic venous insufficient favorably affects fibrinolytic potential and platelet activation. Blood Coagul Fibrinolysis 1996;7:437-46. [abstract]
15. Cahan MA, Hanna DI, Wiley LA, Cox DK, Killewich LA. External pneumatic compression and fibrinolysis in abdominal surgery. J Vasc Surg 2000:32:537:43.
16. Comerota AJ, Katz ML, White JV. Why does prophylaxis with external pneumatic compression for deep vein thrombosis fail? Am J Surg 1992;164:265-8.
17. Stannard JP, Harris RM, Bunknell AL, Cossi A, Ward J, Assington ED. Prophylaxis of deep venous thrombosis after total hip arthroplasty by using intermittent compression of the plantar venous plexus. Am J Orthop 1996;25:127-34. [abstract]
18. Turpie AGG, Hirsh J, Julian D, Johnson J, Gent M. Prevention of deep vein thrombosis in potential neurosurgical patients: a randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. Arch Intern Med 1989;149:679-81.
19. Maxwell GL, Synan I, Dodge R, Carroll B, Clarke-Pearson DL. Pneumatic compression versus low molecular weight heparin in gynecologic oncology surgery: a randomized trial. Obstet Gynecol 2001;98:989-95.
20. White RH, Gettner S, Newman JM, Trauner KB, Romano PS. Predictor of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. N Engl J Med 2000;343:1758-64.
21. Becker DM, Philbrick JT, Selby JB. Inferior vena cava filters. Indications, safety, effectiveness. Arch Intern Med 1992;152:1985-94.
22. Wille-Jorgensen P, Rasmussen MS, Andersen BR, Borly L. Heparins and mechanical methods for thromboprophylaxis in colorectal surgery. Cochrane Database Syst Rev 2003:CD001217. [PubMed]
23. Kearon C, Hirsh J. Starting prophylaxis for venous thromboembolism postoperatively. Arch Intern Med 1995;155:366-72.
24. Koch A, Bouges S, Dinkel H, Ziegler, Dinkel H, Daures JP, et al. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. Br J Surg 1997;84:750-9.
25. Boshkov LK, Warkentin TE, Hayward CP, Andrew M, Kelton JG. Heparin-induced thrombocytopenia and thrombosis: clinical and laboratory studies. Br J Haematol 1993;84:322-8.
26. Hirsh J, Levine MN. Low molecular weight heparin. Blood 1992;79:1-17.
27. Bounameaux H, Huber O, Khabiri E, Schneider PA, Didier D, Rohner A. Unexpected high rate of phlebographic deep venous thrombosis following elective general abdominal surgery among patients given prophylaxis with low-molecular-weight heparin. Arch Surg 1993;128:326-8.
28. Hull R, Raskob G, Pineo G, Rosenbloom D, Evans W, Mallory T, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium prophylaxis against deep-vein-thrombosis after hip or knee implantation. N Engl J Med 1993;329:1370-6.
29. Francis CW, Pellegrini Jr VD, Leibert KM, Totterman S, Azodo MN, Harris HM, et al. Comparison of two warfarin regimens in the prevention of venous thrombosis following total knee replacement. Throm Haemost 1996;75:706-11.
30. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Adnerson FA Jr, et al. Prevention of venous thromboembolism. Chest 2001; 119(1 Suppl): 132S:175S.
31. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000;355:1295-302.
32. Atik M. Dextran 40 and dextran 70: a review. Arch Surg 1967; 94:664-72.
33. Eriksson BI, Wille-Jorgensen P, Kalebo P, Mouret P, Rosencher N, Basch P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolism complications after total hip replacement. N Engl J Med 1997;337:1329-35.
34. Goldhaber SZ. Pulmonary Embolism 1998;339:93-104.
35. Dahl EO, Andreassen G, Aspelin T, Muller C, Mathiesen P, Nyhus S, et al. Prolonged thromboprophylaxis following hip replacement surgery-results of a double-blind, prospective, randomized, placebo-controlled study with dalteparin. Throm Haemost 1997;77:26-31.