Assessment of the Risk and the Prophylaxis of Venous Thromboembolism in Surgical Patients

David Bergqvist

Department of Surgical Sciences, Section of Surgery, University of Uppsala, Sweden

Key Words

Thrombosis · Prevention · Surgery · Low-molecular weight heparin · Fondaparinux · Ximelagatran

Abstract

This review article first deals with risk factors for developing postoperative venous thromboembolism. The various pharmacological prophylactic methods available today are summarized with focus on dominating method low molecular weight heparin and the two new ones, the Xa inhibitor fondaparinux and the IIa inhibitor ximelagatran, both approved in orthopaedic surgery. The optimal timing to start prophylaxis is between 2 hours before and 10 hours after surgery. Evidence is accumulating that some in risk groups prolonged prophylaxis is indicated, ie. elective hip surgery, probably hip fracture surgery and probably also patients operated on for abdominal/pelvic cancer.

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In patients undergoing surgery often two or three of the pathophysiological cornerstones of Virchow's triad are altered in a thrombogenic direction: venous stasis during anaesthesia and immobilization, changes in the haemostatic system with activation of the platelet function and coagulation simultaneously with a decreased fibrinolytic activity and at least during some procedures such as orthopaedic surgery of the hip and knee or extensive pelvic dissection endothelial damage. Several risk factors or risk markers have been reported such as type of surgery, increasing age, surgery for malignant disorders, immobilization, previous venous thromboembolism, hyperestrogenemia, varicose veins, preoperative trauma and various biochemical thrombophilic factors such as insufficiency of antithrombin, protein C and S, activated protein C resistance (factor V Leiden mutation). One important task is to select the risk patients who are in need of prophylaxis to prevent postoperative venous thromboembolism (VTE). There are some models based on consensus meetings or analyses of existing evidence. They come to basically very similar recommendations. Table 1 summarizes and synthesises risk group classification with estimated thromboembolic complications without prophylaxis on which to base conclusions and recommendations on use of prophylaxis. In Table 2 is seen the most important risk factors. To optimise prophylaxis it seems of value to have simple written recommendations on what to use and when to use it.

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David Bergqvist, MD, PhD, FRCS
Department of Surgical Sciences, Section of Surgery,
University of Uppsala,
751 85 Uppsala, Sweden

Tel: +46 18 611 46 33; Fax: +46 18 611 46 32;
E-mail: david.bergqvist@surgsci.uu.se

Table 1. Levels of risk for postoperative venous thromboembolism in patients without prophylaxis [33].

Level of risk / Examples	Calf DVT, %	Prox. DVT, %	Clinical PE, %	Fatal PE, %	Successful prevention strategies
Low risk Minor surgery in patients <40 yr with no additional risk factors	2	0.4	0.2	<0.01	No specific prophylaxis Early and "aggressive" mobilization
Moderate risk Minor surgery in patients with additional risk factors Surgery in patients aged 40-60 yr with no additional risk factors	10-20	2-4	1-2	0.1-0.4	LDUH q12h, LMWH (<3.400 U daily), GCS or IPC
High risk Surgery in patients >60 yr, or age 40-60 with additional risk factors (prior VTE, cancer, molecular hypercoagulability)	20-40	4-8	2-4	0.4-1.0	LDUH q8h, LMWH (>3.400 U daily) or IPC
Highest risk Surgery in patients with multiple risk factors (age>40, cancer, prior VTE); Hip or knee arthroplasty, hip fracture surgery Major trauma, spinal cord injury	40-80	10-20	4-10	0.2-5	LMWH (>3.400 U daily), fondaparinux, oral vitamin K antagonists (INR 2-3) or IPC/GCS + LDUH/LMWH

Table 2. Most important risk factors for development of postoperative deep vein thrombosis.

age
immobilization
trauma
malignancy
varicose veins
estrogen treatment
thrombophilia

Table 3. Thromboprophylactic pharmacological substances with a documented effect and approval.

oral vitamin K antagonists
dextran
heparin
low molecular weight heparins
fondaparinux
ximelagatran/melagatran

What to Use?

In Table 3 is shown the thromboprophylactic substances, which are available today and where there is clear documented evidence of an effect. The dominating method today is to use one of the several commercially available low molecular weight heparins. They differ in how they are fragmented from unfractionated heparin (Table 4). Those differences lead to differences in mean molecular weight, the relative inhibition of activated factor II and activated factor X as well as to some differences in various biological test systems. However, there is no strong indications that those differences lead to different clinical effects concerning thromboprophylaxis. At least, to show such potential differences would require randomised studies of quite considerable sample sizes and the question is if this is of practical inter-

est. There are several metaanalyses and systematic reviews showing that unfractionated low dose heparin is superior to no prophylaxis both preventing deep vein thrombosis (DVT) and fatal pulmonary embolism as well as total peri-operative death [1, 2] as well as showing that low molecular weight heparins are not inferior to unfractionated heparin in these respects [3-10]. There are some indications that low molecular weight heparins are in fact better [5, 6], but anyhow they are at least more practical as administration once daily is enough. The effect is clear both in general and orthopaedic surgery although the relative effect is less in orthopaedic surgery. In a recent Cochrane analysis comparing either unfractionated heparin or low molecular weight heparin to placebo or no treatment in patients undergoing colorectal surgery, the heparins were significantly better than no treatment in preventing VTE (OR 0.32, 95% CI 0.20-0.53). [11]. Direct comparison between unfractionated heparin and low molecular weight heparins showed them to be equally effective (OR1.01, 95% CI 0.67-1.52).

Dextran is equal to low dose heparin concerning prevention of fatal pulmonary embolism but not as effective when it comes to DVT [12]. This effect could, however, be of importance when it comes to the choice of a substance to be used in day care surgery or surgery with extremely short hospitalisation duration.

In recent years two new pharmacological principles have been extensively evaluated in orthopaedic surgery. They are also of theoretical interest as they show that it is possible to reach to a good prophylactic effect by inhibiting certain single factors within the coagulation system - activated factor X and activated thrombin.

In 1979-80 Lindahl et al [13, 14] discovered the antithrombin binding site of the heparin molecule to be a

Preparation	Method of Preparation	Mean Molecular Weight	anti Xa/anti IIa
Ardeparin (Normiflo)	Peroxidative depolymerization	6,000	2
Dalteparin (Fragmin)	Nitrous acid depolymerization	6,000	1,9 - 3,6
Enoxaparin (Lovenox)	Benzylation and alkaline depolymerization	4,200	3,3 - 5,3
Nadroparin (Fraxiparine)	Nitrous acid depolymerization	4,500	2,5 - 4,0
Reviparin (Clivarine)	Nitrous acid depolymerization	4,000	>3
Tinzaparin (Innohep)	Heparinase digestion	4,500	1,5-2,5

Table 4. Comparison of LMWH preparations.

well defined pentasaccharide, which then was synthesized by Choay et al [15], now being clinically available as fondaparinux. In an extensive study programme it has been shown to be significantly better than low molecular weight heparin to prevent venographically postoperative DVT after elective hip and knee surgery and hip fracture surgery [16]. A similar beneficial effect has also been found in patients undergoing abdominal surgery (Agnelli, Bergqvist, Cohen, Geerts PEGASUS unpublished data).

Several studies have shown the thrombin inhibitor recombinant hirudin to be prophylactically effective but for various reasons this has not lead to a wide-spread clinical use. However, there has been intensive research to synthesize thrombin inhibitors, also with an effect after oral administration. Leader in this field has been the oral prodrug ximelagatran, which is metabolised to the active compound melagatran, which also can be used parenterally [17, 18]. Also this substance has been extensively evaluated in orthopaedic surgery, with an effect equal to or better than low molecular weight heparins [19, 20]. Interestingly enough it is absorbed after oral administration already on the third postoperative day after major abdominal surgery [21]. Therefore, prophylactic studies on this group of patients are eagerly awaited.

When to Start?

Of all the prophylactic studies performed the vast majority have studied preoperative start, in most of them the first dose being given a couple of hours before the operation. After a randomised study it was shown that starting prophylaxis in the evening before surgery was effective [22], quite a few investigators used preoperative start the day before surgery. On the other hand, especially in the USA there has been a clear tendency to start postoperatively (18-24 h), primarily because of the fear of bleeding complications. All options seem to be effective and the question is when the optimal time for the first injection is. There is only one randomised study in elective hip surgery, the conclusion being that at least preoperative and postoperative start with dalteparin was equally effective and both significantly better than warfarin which was given in a third arm of the study [23]. This observation led the authors to perform an analy-

sis of the problem from all published studies, where the starting time was given [24]. From this analysis it was concluded that the optimal interval to start prophylaxis, both from a benefit and a risk perspective, was between around 2 hours preoperatively and 10 hours postoperatively.

When to Stop?

In the majority of prophylactic trials the duration of prophylaxis has been around one week. However, it has been known since long that fatal pulmonary embolism may occur up to at least 4-6 weeks postoperatively [25] and the question has been raised if this is due to immediate postoperative DVT or if some patients do develop DVT later with a risk for a later embolism. In 1988 Scurr et al [26] published a study supporting the latter assumption. In abdominally operated patients with a negative phlebography at discharge around 25% developed DVT after discharge (fibrinogen uptake test and plethysmography used for diagnosis). Knowing that patients undergoing elective hip surgery have a prolonged coagulation activation and a decreased venous emptying for a few weeks and also have isolated proximal DVT, where the femoral vein endothelium is locally damaged, we suggested performing a study on prolonged or extended prophylaxis [27]. In fact, we were able to show prolonged prophylaxis (around one month) to be significantly better than standard prophylaxis for around one week to prevent venographic DVT as well as clinical VTE [28]. This was verified in several studies which have been reviewed in two metaanalyses [29, 30] it was clearly shown that the effect was not only on venographic endpoint but also on clinical venous thromboembolism. One study has been performed in hip fracture surgery, showing a highly significant benefit when fondaparinux was used for one month compared to one week [31]. In a study of similar design it was shown that prolonged prophylaxis was also significantly better than in hospital prophylaxis in patients undergoing abdominal/pelvic surgery for malignant disorders [32]. More studies are needed on prolonged prophylaxis in non-orthopaedic surgery but preliminary data seem to verify the observation.

Conclusion

It is today possible to define risk factors for the development of postoperative VTE, thereby giving the possibility to recommend prophylactic measures aiming to prevent these complications, fatal pulmonary embolism inclusive. In modern prophylactic methods it is possible to reach the prophylactic effect with a reasonable risk in form of bleeding complications. Those are, however, rare and in many stud-

ies not more prevalent than in placebo groups. Data are accumulating indicating that postoperative start of prophylaxis seems a reasonable option if done within 10 hours postoperatively. Prolongation of prophylaxis should be seriously considered in patients undergoing hip surgery and may also be used after abdominal/pelvic cancer surgery. For prolonged prophylaxis an oral substance would be an advantage.

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