The optimum duration of low molecular weight heparin for thromboembolism prevention in high risk orthopedic surgery

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ABSTRACT

For patients undergoing hip and knee surgery, the optimum duration of prophylaxis with Low Molecular Weight Heparin (LMWH) is controversial. This paper takes a critical look at the evidence for extending the duration of administration of LMWH beyond the currently recommended 7 to 10 days.

Among the papers reviewed the only consistent benefit associated with prolonged LMWH prophylaxis (duration of 4 to 5 weeks post operatively) was a reduction in venographically detected deep vein thrombosis. Clinically relevant endpoints such as symptomatic thromboembolism (2 to 18%), pulmonary embolus (less than 7%) and death (less than 1%) were unaffected by extending the administration of LMWH. Unanswered questions remain about the safety of 4 to 5 weeks of LMWH at doses used in Canada for this indication. Extended LMWH prophylaxis increases drug costs by approximately 3-fold. The added expense is $153 to $254 per patient depending on the medication used. The cost effectiveness of prolonged LMWH prophylaxis relative to the current recommended duration has not been determined.

In summary, continued prophylaxis with a LMWH beyond 7 to 10 days should not be widely endorsed until it can be demonstrated that the regimen provides clinical benefits at a reasonable cost.

Keywords: duration, Low Molecular Weight Heparin, orthopedic surgery, thromboprophylaxis

RÉSUMÉ

La durée maximale du traitement prophylactique à l'héparine de faible poids moléculaire (HFPM) chez les patients qui doivent subir une chirurgie du genou ou de la hanche est controversée. Cet article brosse un portrait critique des observations sur lesquelles on se fonde pour prolonger la durée du traitement à l'HFPM au-delà des 7 à 10 jours actuellement recommandés.

Parmi les articles passés en revue, le seul avantage récurrent associé au traitement prophylactique prolongé à l'HFPM (durée de 4 à 5 semaines après l'opération) était une diminution des thromboses veineuses profondes visibles à la vénographie. Les paramètres pertinents du point de vue clinique, telles la thromboembolie symptomatique (2 à 18 %), l'embolie pulmonaire (moins de 7 %), et la mortalité (moins de 1 %) n'ont pas été affectés par la prolongation de la durée du traitement à l'HFPM. Des questions demeurent toujours sans réponse relativement à l'innocuité du traitement à l'HFPM d'une durée de 4 à 5 semaines, aux doses utilisées au Canada pour cette indication. Le traitement prophylactique à l'HFPM accroît le coût des traitements médicamenteux d'un facteur d'environ 3. Les dépenses supplémentaires se chiffrent à 153 à 254 $ par patient, selon le médicament utilisé. Le rapport coût/efficacité du traitement prophylactique à l'HFPM quant à la durée actuelle recommandée n'a pas été établi.

En résumé, le traitement prophylactique de longue durée à l'HFPM au-delà de 7 à 10 jours ne devrait pas être utilisé systématiquement, du moins jusqu'à ce que des études aient démontré que ce régime thérapeutique offre des avantages cliniques à un coût raisonnable.

Mots clés : chirurgie orthopédique, durée, héparine de faible poids moléculaire, thromboprophylaxie

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INTRODUCTION

Physiological changes which occur during hip and knee surgery including hypercoaguability, stasis of blood, and damage to the vessel wall endothelium can contribute to the formation of venous thrombi.[1,2] If no preventative measures are taken in these surgical patients, the incidence of deep vein thrombosis (DVT) may be as high as 40 to 60% and fatal pulmonary embolism (PE) may occur in 0.5 to 2% of cases.[2] It has been well documented that a low molecular weight heparin (LMWH) such as dalteparin,[3] enoxaparin,[4,5,6] nadroparin,[7,8] or tinzaparin[9,10] initiated either just before or just after surgery reduces the incidence of thromboembolism in patients undergoing high-risk orthopedic surgery. However, the optimum duration of anticoagu-

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lant prophylaxis with these agents is controversial. Based on the results of the early clinical trials it has been suggested that the drug should be administered for 7 to 14 days. Others have recommended that prophylaxis with LMWH should continue for several weeks following discharge from hospital.[2] The American College of Chest Physicians (ACCP) consensus statement on prevention of thromboembolism recommends that the duration of anticoagulation prophylaxis with LMWH for hip and knee arthroplasty should be 7 to 10 days, regardless of the length of hospital stay. The authors acknowledged the controversy around the duration of therapy and made the recommendation pending the results of further clinical trials.[11] This paper takes a critical look at the evidence for extending the duration of administration of LMWH for DVT prevention in high risk orthopedic surgery patients.

DISCUSSION

In some, but not all, of the previously mentioned clinical trials, investigators recorded the incidence of late DVT. For those patients treated with a LMWH only while in hospital the reported incidence of clinically significant thrombosis (DVT and PE) following discharge from hospital was 0.9 to 1.5% in knee arthroplasty patients[4,5], 0.5 to 1.8% in hip arthroplasty patients[6,9] and 0.4% in a trial that combined the results of hip and knee arthroplasty patients.[10] In these studies, the duration of therapy with LMWH ranged from 7 to 14 days and the duration of surveillance for thrombotic complications following surgery ranged from 30 days to 6 months. Patients were not routinely screened by duplex ultrasonography or venography during the post discharge surveillance period. Symptoms of thrombosis reported by the patient triggered further investigation to objectively confirm a thrombosis. For some patients there are no symptoms associated with the DVT.[1,12] Therefore, the results of the early clinical trials represent the incidence of clinically significant DVTs. In order to objectively detect the presence of DVT, researchers have used compression ultrasonography and venography and it has been suggested that the latter method is a more sensitive method for detecting DVTs in asymptomatic patients.[12]

A study in which routine screening for DVT included duplex ultrasonography (monthly for 3 months) it was reported that the incidence of proximal DVT following discharge from hospital in hip arthroplasty patients who received a LMWH for anticoagulant prophylaxis during hospitalization may be almost 11%.[13] In this study 38 patients (35 with normal bilateral venograms), were treated with heparin 5000 units subcutaneously ever 8 hours (n= 11), enoxaparin 30 mg twice daily (n=16) and enoxaparin 40 mg subcutaneously once daily (n=11). The duration of anticoagulation was for the length of hospital stay (7 to 10 days). Four cases of venographically confirmed DVT were observed, 2 in the heparin treated group, and 2 in the group given enoxaparin 30 mg twice daily. From this relatively small study the incidence of objectively confirmed DVT at 10.5% was higher than the 1 to 2% incidence of clinically significant thromboembolism previously reported. The authors acknowledge that the sample size was too small to accurately determine the magnitude (Confidence Interval = 4 - 25%) and the duration of the risk for thromboembolism following hip surgery. Moreover, there were potential confounding variables. For example, those who suffered a late DVT were on average 10 years older (73 years vs. 63 years of age), than the group that did not have a DVT. Statistical analysis of the differences was not reported. Nonetheless, based on the observed incidence of late DVT, the authors suggested that DVT prophylaxis should be extended to include a period of several weeks following hospitalization pending the results of further investigation.

In a review of previously published trials on thromboprophylaxis in orthopedic surgery, Ricotta and colleagues summarized the incidence of clinically significant thrombosis in patients who were negative for DVT on discharge and who received a LMWH or other anticoagulant for DVT prophylaxis while in hospital[14]. The prevalence of post-discharge, clinically overt DVT among participants who were negative for DVT prior to discharge from hospital (bilateral venography) was found to be about 1.5%. The authors concluded that it is unnecessary to extend the duration of prophylaxis and suggested that anticoagulant prophylaxis may be discontinued for patients who do not have a DVT prior to discharge from hospital as documented by ultrasonography or venograms. They go on to recommend that efforts should be directed at developing a noninvasive alternative to venography for detecting DVT in orthopedic surgery patients.

The conclusion from the review by Ricotta and colleagues has been supported by the results of a large trial in which objective screening confirmed that in hip and knee surgery patients clinically significant DVT following discharge from hospital is a relatively rare occurrence once appropriate prophylaxis is employed.[15] In a multicenter study the incidence of postoperative thromboembolism and side effects such as major bleeds was measured in a cohort of 1984 patients who had hip and knee replacement. All patients receive enoxaparin 30 mg subcutaneously twice daily for 5 to 14 days (mean duration 9 days) and all were screened by compression ultrasonography. The reported incidence of objectively confirmed DVT was 4.1%. There were 55 DVTs and 27 PEs, 3 of which were fatal. The incidence of sympto-

matic thromboembolism was 2%. Two of the 3 fatal PEs occurred within the first 2 postoperative days. One of the 3 deaths was deemed preventable by extended prophylaxis. The incidence of major hemorrhage was 2.9%. On the basis of these findings, the authors concluded that extending the duration of prophylaxis with a LMWH beyond 9 days would not yield any significant clinical benefits.

While the majority of evidence indicates that adequate prophylaxis with a LMWH for about 9 days following hip and knee surgery is associated with an incidence of late thromboembolism of about 2% what is the evidence that extending the duration prophylaxis would benefit the patient and at what cost. Summarized in Table I are the results of 3 clinical trials which have investigated the influence of the duration of anticoagulation prophylaxis with a LMWH on the risk for venous thrombosis following orthopedic surgery. In 1 of the double-blind studies subcutaneous enoxaparin 40 mg or placebo was administered once daily for 21 days following discharge from hospital.[16] While in hospital all patients received active drug for DVT prophylaxis for 13 to 15 days after total hip replacement surgery and were screened using bilateral venograms to rule out the presence of DVT prior to discharge. All patients were screened a second time with bilateral venograms at 35 plus or minus 2 days following surgery. Of the 179 patients enrolled, 5 in the enoxaparin group and 1 in the placebo group were ex-

Table I. Summary of thrombosis prevention trials with extended duration of low molecular weight heparin

Surgery[m]	Drug Regimen (N=number of subjects)	Bilateral venograms (n=evaluable subjects)	Symptomatic TE [Ψ]	DVT[Φ]	Proximal DVT[Ω]	PE[π]	Major Bleed[#]	Minor Bleed[λ]	Death
Total Hip Replacement[16]	Enoxaparin 40mg SC daily X 13 to 15 days (N=89)	At day 13 to 15 and at day 34 to 36. (n=88)	16/88 (18%)	17/88 (19%)	7/88 (8%)	0/88	0/89	4/89 (5%)	0/89
	Enoxaparin 40mg SC daily X 35 days (N=90)	At day 13 to 15 and at day 34 to 36. (n=85)	14/85 (16%)	6/85 (7%) p=0.018	5/85 (6%)	0/85	0/90	17/90 (19%)	0/90
Total Hip Replacement[18]	Enoxaparin 40mg SC daily X 11 days (N=131)	At day 31 (n-116)	10/116 (7%)	45/116 (39%)	28/116 (24%)	2/116 (2%)	4/131 (3%)	1/131 (0.8%)	0/131
	Enoxaparin 40mg SC daily X 31 days (N=131)	At day 31 (n-117)	2/117 (2%)	21/117 (18%) p<0.01*	8/117 (7%) p<0.01	0/117	2/131 (2%)	6/131 (5%)	0/131
Total Hip Replacement[19]	Dalteparin 5000 U SC daily X 7 days (N=131)	At day 7 and to day 35 (n=89)	3/104 (3%)	23/89 (26%)	9/89 (10%)	7/105 (7%)	–	–	1/131 (0.8%)
	Dalteparin 5000 U SC daily X 35 days (N=134)	At day 7 and to day 35 (n=93)	4/114 (4%)	11/93 (12%) p=0.034	4/93 (4%)	4/111 (4%)	–	–	1/134 (0.8%)

[m]All trials were prospective, randomized, placebo controlled and double blind in design.
[Ψ]Symptomatic TE is the incidence of clinically overt deep vein thrombosis (DVT) or pulmonary embolism (PE) confirmed by venography in the case of DVT or ventilation perfusion scan or pulmonary angiography in the case of PE.
[Φ]Total DVT is incidence of venographically demonstrated thrombosis in the deep veins of the leg either above or below the knee.
[Ω]Proximal DVT is the incidence of venographically demonstrated thrombosis in the deep veins of the leg.
[π]PE is the incidence of PE confirmed by intermediate or high probability ventilation perfusion scans or pulmonary angiography or at autopsy
[#]Major bleed is the incidence of hemorrhage resulting in a decrease in hemoglobin concentration of 20 G/L, or requiring transfusion of 2 units of packed red cells or hemorrhage into the retroperitoneal or intracranial space or requiring reoperation.
[λ]Minor bleed is the incidence of a bleed not meeting the criteria for major bleed.
*The p value is given where the difference between the study and control groups was reported in the original study to be statistically significant i.e less than 0.05.

cluded because they did not have a second bilateral venogram. Clinical assessment was done 3 months later. During the 3-week follow-up period after discharge, the incidence of symptomatic DVT at 16% with prolonged enoxaparin versus 18% for the controls was similar in the two treatment arms. The overall incidence of DVT in the extended prophylaxis group (7.1%) was significantly less than that for the placebo group (19.3%). While distal DVT (1.2 vs. 11.4%) occurred less frequently there was no difference in the incidence of proximal DVT in the study group as compared to the control group (5.9 vs. 7.9 %, respectively) who received LMWH only for the duration of hospital stay. There were no cases of PE nor were there any deaths in the study. Of those receiving extended prophylaxis, 18.9% experienced minor bleeds as compared to 4.5% in the controls, the majority of which was bruising at the injection site. No episodes of major bleeding were reported in either group. While there were fewer venographically proven DVTs in the group receiving prolonged prophylaxis there was no difference in proximal DVT, PE or symptomatic DVT. Some investigators have suggested that an asymptomatic DVT detected venographically is a surrogate endpoint with little clinical relevance.[14,17] Therefore, the clinical significance of the study results is questionable. While acknowledging this limitation the authors concluded that extended prophylaxis with enoxaparin is safe and effective at reducing the risk for late DVT in hip arthroplasty patients.

In another trial involving hip arthroplasty patients, enoxaparin 40 mg subcutaneously once a day for the duration of hospital stay (mean of 11 days) was compared with extended prophylaxis for 1 month (10 days in hospital and the balance of the time in the community).[18] The incidence of venographically confirmed thrombosis during the post-discharge period was significantly lower in the group that was treated for 1 month (18%) as compared with the group that received prophylaxis only while in hospital (39%). Proximal DVT was also less frequent in the study group (7%) relative to the controls (24%). Whereas, there were no cases of PE in the group treated for 1 month, there were 2 cases of PE in the control group. There were no significant differences in adverse drug effects reported. There was a 5% incidence of injection site hematoma observed among the 117 enoxaparin treated patients. There were no reports of major bleeding related to treatment.

Patients were not objectively screened for DVT prior to discharge from hospital and randomization to long-term prophylaxis, therefore, it is not known if the thrombosis occurred during hospitalization or at a later date. LMWH at doses for DVT prevention have been found to halt the progression of thrombosis and contribute to thrombolysis.[19] One cannot rule out the possibility that at randomization there was a similar incidence of asymptomatic thrombosis in the two groups but that more cases resolved in the enoxaparin arm , and thus, fewer were detected by venogram at 1 month following surgery. The authors noted that while there may be a benefit by way of fewer thromboembolic complications with extended enoxaparin under the regulated setting of a clinical trial where compliance is assured, it is unclear whether or not these findings can be extrapolated to clinical practice. They also point out that it is uncertain whether or not the longer duration of prophylaxis is cost-effective and suggest that further study is needed to address this question.

In the third prospective, randomized, double-blind placebo controlled trial, efficacy and safety of prophylaxis with dalteparin 5000 units subcutaneously once daily for 35 days (N=134) was compared with the same therapy for 7 days (N=131) in hip replacement surgery patients.[19] Among those receiving dalteparin for 7 days, the incidence of DVT was 26% which was significantly greater than that observed among those who were on prophylaxis for 35 days (12%). There were no significant differences in the incidence of symptomatic DVT (3 vs. 4%) or in proximal DVT (10 vs. 4 %) or PE (7 vs. 4 %) with 7 days vs. 35 days of drug. There were 2 deaths in this study. One was associated with a fatal PE among the controls and the other was associated with a subdural hematoma in a patient who was in the extended prophylaxis group. From the results of their study, the authors recommended that in hip arthroplasty patients prophylaxis with dalteparin 5000 units subcutaneously once daily should be continued for 5 weeks following surgery. However, it should be noted that as with the previous studies the benefit of extended duration of LMWH was in the reduction of asymptomatic DVT with no clinically significant differences in outcome noted.

From the results of 3 extended LMWH prophylaxis trials[16,18,19] there was a consistent finding of significantly fewer DVTs as detected by venogram, most of which were asymptomatic. Continuing with prophylaxis regimens of a LMWH for 4 to 5 weeks after hip surgery made no difference to the incidence of symptomatic DVT or PE. In addition, no advantage by way of reduced mortality was demonstrated. In other words, the clinical significance of any potential benefits associated with prolonged LMWH prophylaxis following high-risk orthopedic surgery is questionable.

There are a number of other questions that remain unanswered. While the trials to date have been on hip surgery patients, the potential benefits and risk of extended LMWH prophylaxis following knee surgery is unknown. Also, can the results of the studies with enoxaparin be extrapolated to the Canadian setting where the recommended dose is 30 mg twice daily rather than

40 mg daily?[20] Dose comparative trials with enoxaparin have yielded conflicting results as to whether or not a dose of 30 mg twice daily is superior to 40 mg once daily for DVT prevention in hip surgery.[6,21] The issue of safety is also unresolved in light of the lower bleeding rate reported with the smaller dose of enoxaparin.[6] It remains to be determined whether or not extending the duration of prophylaxis at the higher dose of enoxaparin (30 mg twice daily) commonly used in clinical practice today will influence effectiveness and safety. The potential benefits and risks of extended prophylaxis have not been investigated with all the LMWH currently on the market in Canada. No clinical trials for tinzaparin and nadroparin were available. Can the results with enoxaparin and dalteparin from the extended prophylaxis trials be generalized to other agents such as tinzaparin and nadroparin? Finally, the added cost of extended prophylaxis with a LMWH must also be considered as these are relatively expensive agents. Does prolonged prophylaxis for high-risk orthopedic surgery make economic sense? The drug cost of DVT prevention with a LMWH for 10 days ranges between $73 and $121 depending on the agent. (Table II) Changing the duration of a LMWH to 1 month would triple the costs for thromboembolism prevention. For some patients this can mean an added cost of $153 to $254 for the drug alone. Pharmacoeconomic studies are needed to determine whether or not prolonged prophylaxis with a LMWH is a cost-effective strategy.

Table II. Cost comparison of the low molecular weight heparin regimens for the prevention of thrombosis

Drug; unit cost[Φ]	Daily dose[π]	Cost for 10 days[Ω]	Cost for 31 days
Dalteparin 5000 unit syringe; $7.50	5000 units	$75	$232.50
Enoxaparin 30 mg syringe; $6.04	60 mg	$120.80	$374.48
Nadroparin 3800 unit syringe; $8.95	3800 units	$89.50	$277.45
Tinzaparin 4500 unit syringe; $7.26	4500 units	$72.60	$225.06

[Φ]Unit cost is the acquisition cost for drug according to hospital contract prices as of July 1998.
[π] Daily dose is the commonly recommended dose by the manufacturer for the prevention of deep vein thrombosis following high risk orthopedic surgery
[Ω]Cost is calculated as the number of doses for 10 or 31 days times the unit cost.

CONCLUSION

In conclusion, for patients undergoing high risk orthopedic surgery administration of a LMWH for 10 to 14 days is associated with an incidence of clinically significant thromboembolism following discharge from hospital of 3 to 18% over 3 months. Continuing the administration of LMWH for 4 or 5 weeks after hip surgery has resulted in a reduced incidence of objectively measured DVT but has not improved clinically relevant outcomes such as symptomatic DVT, PE, or mortality rates. Also, further studies are needed to determine whether or not extended LMWH prophylaxis is a cost-effective use of resources. Prolonged prophylaxis with a LMWH beyond the current recommended duration should not be widely endorsed until it can be demonstrated that this strategy provides clinical benefits at a reasonable cost.

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