Research Article

Low molecular weight heparin in prophylaxis of deep vein thrombosis in Asian general surgical patients: A Kashmir experience

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Abstract

Background and Objectives: Deep vein thrombosis (DVT) occurs at a lower rate in Asia than in the rest of the world. We wanted to study the significance and efficacy of low molecular weight heparin (LMWH) in prophylaxis of DVT in major general surgical patients in the Kashmir Valley (India, Asia) so as to make it a routine in our patients. **Patients and Methods:** This was a prospective study in which the effect of LMWH was compared with no prophylaxis. **Results:** LMWHs are more effective than no prophylaxis in the prevention of DVT and pulmonary thromboembolism in highest-risk general surgical patients (odds ratio = 16.64; 95% confidence interval = 3.63–1130.03; *P*-value = 0.014). **Conclusion:** LMWHs have a significant prophylactic effect on DVT in general surgical patients, with a higher benefit to risk ratio, and, in spite of the low incidence of DVT in Asia, its prophylaxis should routinely be considered in this part of the world as well, preferably in the form of LMWHs.

Keywords: Heparin, prophylaxis, thrombosis

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Introduction

Deep vein thrombosis (DVT) most commonly occurs in calf veins, and its most feared complication is pulmonary thrombo-embolism (PTE).[1] The incidence of DVT in the absence of prophylaxis is 16%,[2] 25%[3] and 16–26% (in colorectal surgeries).[4,5] PTE following lower limb DVT is responsible for 10% of all hospital deaths.[6] The most common risk factors are major surgical procedures, especially hip replacement, and major abdominal surgeries.[7] Malignancy is known to cause DVT because of hyperfibrogenemia.[6,8] The most common symptom of DVT is pain in the calf[8] and the most significant sign is tenderness in the calf with ankle edema.[6] Duplex ultrasonography (USG) is the investigation of choice to diagnose DVT because it is a noninvasive and hazard-free method.[6]

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Prevention of DVT should begin before the induction of anesthesia, as the thrombotic process begins intraoperatively and even before surgery in those with acute conditions.[9] Heparins have emerged as the agents of choice for DVT prophylaxis. Low molecular weight heparins (LMWHs) have replaced unfractionated heparin (UH) in many hospitals because of their many advantages[10] over the later, like they have superior or comparable efficacy and safety, they have very less risk of bleeding because of low immunogenicity, they have decreased frequency of thrombocytopenia[11] and osteopenia, they prevent early recurrence of thrombus in the treatment of DVT because they achieve higher quality of anticoagulation in the first hours,[12] they are taken as single daily dose and they do not require activated partial thromboplastin time monitoring.

Materials and Methods

This was a prospective study conducted over 2.5 years from July 2005. A total of 215 highest-risk patients (as per risk score assigned to each risk factor by Caprini *et*

al.)[13] undergoing elective and/or emergency general surgeries were recruited with informed written consent from the patients and approval from the hospital ethical committee. The main risk factors for DVT were documented [Table 1]. All the patients had normal preoperative femoral and popliteal veins on Doppler USG. Three patients were excluded because of low platelet count in two (<140 × 10^6/L) and abnormal coagulogram in one. The patients were randomly grouped under prophylaxis group (n = 104) and control group without prophylaxis (n = 108). Open surgical procedure was performed on every patient. They were matched properly with respect to age, sex, disease type [Table 2], surgical procedure [Table 3] and other risk factors. Enoxaparin 0.4 mL (4000 IU) or nadroparin 0.3 mL (2850 IU) were administered subcutaneously in the anterior abdominal wall to all study group patients 1–2 h before induction of anesthesia and continued once a day till the 7th postoperative day or discharge, whatever was earlier. All the patients were examined daily after surgery and duplex USG was performed on the 7th postoperative day, or on appearance of signs of DVT, by blinded observers. Suspicious clinical findings were confirmed by duplex USG and PTE by ventilation/perfusion scan (v/q ratio). Established DVT was treated by UH in a dose of 80 U/kg intravenous stat followed by 18 U/kg infusion, along with warfarin 5 mg per day till therapeutic INR was achieved (2–2.5). After that, heparin was discontinued and warfarin continued for 6 months. The surgeon blinded to randomization assessed the intraoperative complications, postoperative platelets (PLT s) and blinded observers performed coagulogram on the 1st, 3rd, 5th and 7th postoperative days. Besides, the wound site was examined daily for bleeding and hematoma, and the injection site for pain and bruise. Data were prospectively analyzed by the use of SPSS 11.5 and Java two-way contingency table system, using Yates-corrected Chi square test with P-value <0.05 as significant.

Results

The two groups were matched with respect to their age, sex and other known DVT risk factors [Table 1], diagnosis [Table 2] and surgical procedures [Table 3]. The mean age in years was 57.29 (9.617) years and 55.72 (10.672) years in study group and in the control group, respectively. DVT was significantly reduced by the use of LMWH. Eight of the 108 control group patients developed duplex USG-proven DVT, while none among the LMWH group did so (controls; DVT = 8/108, LMWH; DVT = 0/104, OR [odds ratio] = 16.64, P-value = 0.014). DVT was confirmed by duplex USG, and all the patients were symptomatic for DVT. Pain with ankle edema was the most common symptom (50%) and calf tenderness the most common sign (87.5%). Two of the eight DVT patients died (25%) because of PTE on the 3rd postoperative day, which was documented by duplex USG and ventilation perfusion scan, whereas the remaining six patients responded well to the treatment. Six of the eight DVT patients were more than 60 years of age, while only two were younger than 60 years (OR = 3.4, P = 0.247). All the eight DVT patients were among the malignancy cases (malignancy 8/172, benign 0/40, OR = 3.90, P = 0.352).

The surgeon who was blinded to the randomization did not perceive more difficulty in the LMWH group as compared with controls during the surgery

Table 1: Risk factors for DVT (n = 212)

Risk factor	LMWH group (n = 104)	Control group (n = 108)	P value
Mean age in years	57.29 (9.617)	55.72 (10.672)	0.075
Male/female	50/54	52/56	0.992
Obesity (>20% of ideal BW)	9	8	0.935
Malignancy	84	88	1.000
Postop immobility >72 h	20	17	0.625
Central venous access	1	3	0.641

LMWH: Low molecular weight heparin, DVT: Deep vein thrombosis

Table 2: Diagnosis in the control and LMWH groups (n = 212)

Disease	LMWH	Controls	Total (% age)	P value
Ca stomach/GE junction	36	46	82 (38.7)	0.293
Colorectal carcinoma	46	42	88 (41.0)	0.516
Obstructive jaundice	10	8	18 (8.50)	0.741
Gut perforation with peritonitis	4	4	8 (3.83)	1.000
Others	8	8	16 (7.54)	1.000
Total	104	108	212 (100)	

LMWH: Low molecular weight heparin

Table 3: Surgical procedures in the LMWH and control groups

Procedure	LMWH	Controls	Total (% age)	*P* value
Gastrectomy/esophagogastrectomy	36	46	82 (38.7)	0.293
Hemicolectomy	14	18	32 (15.1)	0.646
APR/LAR	20	16	36 (17.0)	0.501
Segmental resection with E–E anastomosis	14	12	26 (12.3)	0.755
CBD exploration	10	8	18 (8.5)	0.741
Others	10	8	18 (8.5)	0.741
Total	104	108	212 (100)	

APR = Abdominoperineal resection, LAR = Low anterior resection, CBD = Common bile duct, E–E = End to end, LMWH: Low molecular weight heparin

Table 4: Complications and postop hospital stay

Complication	LMWH (*n* = 104)	Controls (*n* = 108)	*P* value
Intraop blood loss (mean) (mL)	238.0	229.6	0.236
Operative time (min)	139.3	147.9	0.113
Intraop bld transfusion (pts)	20	17	
Volume transfused (mean) (units)	3.00	3.2	0.716
Postop drainage (mean) (mL)	317.4	302.7	0.273
Postop PLTs (x1000/dL) (mean)	241.5	235.1	0.428

Pts = Patients, PLTs = Platelets, min = Minutes, bld = Blood, op = Operative, LMWH: Low molecular weight heparin

[Table 4]. Six patients on LMWH and two in the control group developed minor wound-site hemorrhage in the form of small hematomas and minor ooze (P = 0.256); none required blood transfusions, withdrawal of the drug or re-operation.

No significant difference was seen in the type of LMWH used (enoxaparin n = 60, DVT = 0. Nadroparin n = 44, DVT = 0. P = 1.00). Finally, there was no significant difference in the postoperative hospital stay among the two groups (LMWH, mean = 11.7 [4.1] days. Controls, mean = 11.2 [4.0] days. P = 0.400).

Discussion

As per our study, DVT in the Kashmir Valley (Jammu and Kashmir, India) occurs at an incidence equal to or greater than that in other parts of Asia, but lower than that in the rest of the world.[2,14] Our study included highest-risk patients only, and the incidence of DVT was found to be 7.40% without prophylaxis, as compared with 0% in the study group (controls 8/108; LMWH 0/104; OR = 16.64. P = 0.014). This shows that DVT (and PTE) was reduced to 0 by the use of LMWH. Other studies support our results, showing significant reduction of DVT in general surgical patients by the use of LMWH.[14-18] Yik Hong *et al.*,[14] in a randomized controlled trial on Asian patients, found a statistically significant reduction of DVT by the use of enoxaparin as compared with no prophylaxis in high-risk general surgical patients (3% versus 0%. P = 0.045). Mismetti *et al.*[17] in a metaanalysis showed that LMWHs in prophylactic doses provide a 72% reduction in the risk of DVT as compared with no treatment or placebo. Various studies have found LMWH to be effective as UH in the prevention of DVT, but in view of its more convenient way of administration and overall risk benefit ratio, they advocated that LMWHs might be preferred over UH for DVT prophylaxis.[15,19,20]

All the cases of DVT occurred in cancer patients (OR = 3.90, P = 0.352). Although not statistically significant, this shows that cancer patients had 3.90-times more risk of developing DVT than benign cases. Malignancy is an independent risk factor whereas benign diseases need one or more risk factors to increase the risk of DVT.[6,8] Six of the eight DVT patients were >60 years of age (OR = 3.4, P = 0.247), showing a higher likelihood of developing DVT after the age of 60 years , consistent with Gutt *et al.*[3] and Caprini *et al.*,[13] who categorized patients more than 60 years of age in the high-risk group for DVT. An incidence of 17.6% (four in hemicollectomies, two in abdominoperineal resection/low anterior resection, total 6/34), was found in colorectal surgeries without prophylaxis, matching with that of Torgensen *et al.*[4] and Jorgensen *et al.*,[5] who separately found an incidence of DVT equal to 16–26% among colorectal surgeries in the absence of any prophylaxis.

The low incidence of DVT in the Asian population has been shown by many studies; 0.27%,[21] 4.70% and 3.0%,[14] than in the rest of the world.[4,22] The actual cause of the low DVT incidence in Asia is not known; however, the overall low platelet count of people in the Valley has been

documented in our study (<150 X 10^3/dL = 40%; 151–200 X 10^3/dL = 40%; 201–350 X 10^3/dL = 20%), and its possibility of contributing to the low incidence of DVT needs to be proven in the future. Color Doppler has been used in many studies for the diagnosis of DVT[14,2,23] because of its easy availability, cost-effectiveness and hazard-free and noninvasive nature. Pain was the most common symptom in our study (75%), consistent with others,[1] and the most common sign was calf tenderness (75%), followed by ankle edema (50%), consistent with Scurr.[6] Six of the 104 patients on LMWH (5.77%) and two of the 108 (1.85%) patients in the control group developed wound-site hemorrhage in the form of minor ooze and hematoma (P = 0.256); none required withdrawal of the drug, blood transfusion or re-operation. Kakkar[24] and Bergqvist *et al.*[16] found the incidence of wound hematoma as 3.9% and 6.7%, respectively, with none of the patients requiring blood transfusion, re-operation or withdrawal of the drug. Kakker *et al.*[24] also found that there was no significant difference between LMWH and UH in terms of incisional or total blood loss during surgery, postoperative drainage or wound hematoma formation.

No patient developed adverse reactions at the injection site in the form of pain, erythema, inflammation and hemorrhage/echymosis, consistent with the observations of Bergqvist *et al.*[16] No patient developed significant (<140 X 10^3/dL) thrombocytopenia in our study, as shown by Warkentin *et al.*,[11] who found an incidence of 0–9% with the use of enoxaparin.

Conclusion

In spite of the low-DVT incidence in Asian patients, its prophylaxis should routinely be considered in high-risk general surgical patients in this part of the world because of the increased mortality from PTE. And, LMWHs in view of their significant effect, higher benefit to risk ratio and convenience of administration, should preferably be used for this purpose.

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