Low Molecular Weight Heparin versus Aspirin plus Intermittent Compression Devices for Thromboprophylaxis in Indian Patients Undergoing Total Hip and Knee Arthroplasty

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ABSTRACT

Introduction: Thromboembolic complications is common after arthroplasty. The purpose of this study was to find out the incidences of deep vein thrombosis, symptomatic, and fatal pulmonary embolism in Indian patients undergoing arthroplasties and to compare the effectiveness and safety of thromboprophylaxis with low molecular weight heparin versus aspirin plus intermittent pneumatic compression device.

Methods: Patients who had a total hip and knee arthroplasty were randomized to receive prophylaxis with LMWH or aspirin plus intermittent pneumatic compression device. After four to six days, all patients underwent bilateral lower-extremity color Doppler ultrasonography to screen for deep venous thrombi in the calf and thigh. Any clinical symptoms of pulmonary embolism were evaluated with pulmonary CT angiography. Bleeding events in both groups were documented. The patients were followed up at 6 week and 3 months with Color Doppler to look for the evidence of deep venous thrombi.

Results: 300 patients (409 joints) were randomized into 2 groups and studied regarding the incidence of deep vein thrombosis, pulmonary embolism, safety of the thromboprophylaxis in regard to its efficacy. Demographics were similar clinically between the groups. The rate of major bleeding events was 0.67% in the aspirin and compression group and 6% in the low-molecular-weight heparin group. Overall, prevalence of DVT and PE in Indian patients who underwent total hip or knee arthroplasty was 0.67% and 0.33% respectively. The rates of deep venous thrombosis were 1.33%, in the aspirin plus compression group compared 0% in the LMWH group. The rates of pulmonary embolism were 0.67% in the Aspirin plus compression group and 0% in the heparin group, and there were no fatal pulmonary emboli. Within the six week and three month follow-up period, no events occurred. There was no difference between the groups with regard to the prevalence of venous thromboembolism.

Conclusions: An inexpensive multimodal protocol, consisting of aspirin, exercises, and the use of intermittent compression devices, was associated with relatively higher thromboembolic complications. However, major bleeding events were significantly lower in Aspirin group.

Keywords: Aspirin; Deep Vein Thrombosis; Low Molecular Weight Heparine; Pulmonary Embolism.

INTRODUCTION

Total hip and knee arthroplasty are extremely successful orthopedics procedures that relieve pain, improve function, and enhance the quality of patient's lives. However, these procedures are not without complications, the most notable being the risk of morbidity and mortality from the development of venous thromboembolic disease.[1]

Venous thromboembolism may present as distal deep venous thrombosis (DVT), proximal DVT and pulmonary embolism (PE), the last of which in some cases can be fatal.[2] The reported incidence of distal vein thrombosis after Total Knee Arthroplasty (TKA) and Total hip arthroplasty (THA) without prophylaxis is 40%–84%.[3-6]

Chemical prophylactic agents such as aspirin, warfarin, heparin, and pentasaccharides, as well as

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physicalmodalities such as compression stockings and lower extremitypumps are used to minimize the risk of VTE.[8]

The widespread belief that the rate of fatal pulmonary embolism after replacement arthroplasty is more than 1% is based on the findings of few studies conducted mainly in the 1960s and 1970s.[9,10] During the last decade, the incidence of fatal PE has decreased substantially to a rate of 0% to 0.2%.[9,10] This reduction is the result of advancements in anesthesia and surgical technique, our better understanding of the pathogenesis of thromboembolic disease during and after surgery, use of pneumatic compression devices, better pain management, and early mobilization.[10] This incidence appears to be consistent no matter which prophylactic agents are used.[10]

Among Asians, particularly Indian population, it has been said anecdotally that there is a considerably lower prevalence of deep vein thrombosis.[11-13] There are no well documented studies regarding the prevalence of DVT in Indian patients. Without any convincing studies in Indian population, the routine use of thromboprophylaxis for total joint arthroplasty based on western literatures may not be justifiable.

METHODS

The study was prospective randomized controlled trial conducted in the Department of orthopedics, at a tertiary care referral centre. 300 patients were enrolled after informed and written consent and prospectively followed from May 2010 to May 2012 were enrolled, studied, and followed prospectively as per the protocol. Prior approval for the study was obtained from the Institutional Ethics Committee.

All the patients who were scheduled for unilateral or bilateral total hip or knee arthroplasties were included in the study. Exclusion criteria included patients with coagulation or bleeding disorders, hypersensitivity to aspirin or low molecular weight heparin, Heparin induced thrombocytopenia, history of thromboembolic disease/ chronic venous insufficiency, ocular or neurosurgical procedure during last 3 month, active peptic ulcer disease, severe renal insufficiency, systolic hypertension >200 mm Hg, pulmonary tuberculosis, a solid malignancy tumor, active Liver disease, peripheral vascular disease , and who refused to give consent.

A computer-generated randomization schedule was created. The coordinators, surgeons, and the patients enrolled in the study were not blinded to the type of intervention. All the eligible patients were randomized either to receive enoxaparin 40mg once a day s/c 12hours after surgery after removal of epidural catheter (if present) till patient was mobilized (approximately 4th postoperative day) or aspirin 325 mg twice a day for 6 weeks along with intermittent pneumatic compression device applied within 2 hours of surgery till patient was mobilized (approximately 4th postoperative day).

All the patients were operated by a senior orthopedic surgeon of the orthopedic department. For the total hip arthroplasty, the posterior approach was used with the patient in lateral decubitus position. Uncemented acetabular and femoral components were used. For total knee arthroplasty, medial parapatellar midvastus approach was used; and the surgery was done under the tourniquet control. Cemented femoral and tibial components were used for knee arthroplasty.

All patients had a hemovac drain left in place after surgery. Blood loss was measured by weighing sponges in the operative room, direct measurement of hemovac drainage, and daily hemoglobin levels. All drains were removed at 48 hours after surgery or when the per shift drainage was less than 25ml. Bandages were removed on the second postoperative day and physiotherapy was initiated as soon as the drain was removed. Transfusion was ordered if the hemoglobin was less than 80 g/L or if the patient experienced cardiopulmonary symptoms.

Patients in both groups were closely monitored throughout their hospitalization for any potential bleeding complications and for clinical signs and symptoms of deep venous thrombosis or pulmonary embolus. After four to seven days (earlier if clinically indicated), all patients underwent bilateral lower-extremity duplex ultrasonography to screen for deep venous thrombosis. Any clinical symptoms suspicious of pulmonary embolism were evaluated by cardiologist and battery of tests including electrocardiogram, chest x-ray, arterial blood gas analysis, and Pulmonary CT angiography are run. Color Doppler screenings were done by experienced radiologist of Department of Radio-diagnosis. Both cardiologists and radiologists were blinded in respect to the nature of DVT prophylaxis received by the patients.

On the ultrasound examination, the findings were reported as normal study or proximal deep venous thrombosis, distal deep venous thrombosis, or superficial venous thrombosis. Proximal deep venous thrombosis was defined as venous thrombosis in vessels proximal to the popliteal fossa (the common femoral vein, the deep femoral vein, the superficial

femoral vein, and/or the popliteal vein). Distal deep venous thrombosis was defined as thrombosis in vessels distal to the popliteal fossa (the peroneal vein, the anterior tibial vein, and/or the posterior tibial vein). Thrombosis in the saphenous vein was considered to be superficial venous thrombosis. A patient who had distal vein thrombosis on Color Doppler was evaluated daily for symptoms/signs of propagation and PE. Repeat Doppler was done after 4 days and before hospital discharge. A patient with proximal vein thrombosis was treated with Enoxaparin 1mg/kg twice daily (at least for 5 days and discontinued when INR >2 on 2 consecutive measurements at least 24 hrs apart) along with Warfarin 5 mg for period of 3 months. Serial Doppler studies were done to document the resolution of thrombus. If thrombus was found to be propagating or unresolved, CT pulmonary angiography was done.

All patients with a negative scan were followed clinically, for a mean (and standard deviation) of 10 ± 2 weeks, for signs or symptoms of deep venous thrombi, pulmonary emboli, or re-hospitalization because of a complication related to the method of prophylaxis, a bleeding complication, or a wound problem. Repeat Color Doppler of B/L lower extremity was done at 6 ±1 weeks follow up (earlier if clinically indicated).The duration of follow-up was limited to a period of three months. Any thromboembolic complications that may have occurred after the third postoperative month were not considered to be related to the operation and not recorded.

Prophylaxis was interrupted in patients who had complications such as reactions to the drugs, hemorrhage, acute tubular necrosis, venous thrombosis, or pulmonary emboli. Because the study was specifically intended to answer the question of efficacy of the drugs for prevention of fresh thrombi following surgery, and not to determine their efficacy in the treatment of venous thrombi, patients in whom fresh thrombi developed were regarded as failures of prophylaxis and treated.

The primary determinant of efficacy of thromboprophylaxis was the incidence of DVT as determined by Color Doppler study of the bilateral lower extremity and clinical evidence. Clinical evidence included reported DVT /PE as an adverse event or the occurrence of symptoms and signs of thromboembolic disease and associated therapy. Color Doppler diagnosed DVT was primary end point for determination of efficacy of study.

The primary determinants of safety were the incidences of major and minor hemorrhagic episodes. A major hemorrhagic episode was overt hemorrhage associated with anemia that required prolonged hospitalization, anemia with hypotension that required intervention to prevent impairment, bleeding that required any intervention such as surgery or hematoma aspiration to prevent permanent impairment or damage, bleeding that endangered critical organs (intra-cerebral, intraocular, intra-spinal, pericardial, or retroperitoneal), hematoma that required prolonged hospitalization, hematoma that led to joint infection requiring debridement, death or a life-threatening clinical event, postoperative transfusion of more than two units of packed red blood cells, decrease of 20 g/l or more in hemoglobin that is directly attributable to the overt hemorrhagic episode.

Minor bleeding was any bleeding that was not major bleeding (e.g., increased wound drainage reported by the surgeon or a drop in the hemoglobin level not requiring transfusion or prolonged hospitalization). The bleeding index (defined as the number of units of whole blood or packed red blood cells transfused plus the difference between the first hemoglobin value after surgery and the value prior to discharge), a decrease in the hemoglobin level of ≥20 g/l, and the number of units of blood transfused were reported.

We defined "increased wound drainage" as follows: fluid drainage occurring for 4 consecutive days beyond postoperative day 5; drainage that would significantly wet or soak at least or ≥ 2 x 2 area of gauze dressing; and drainage that emanated from the same specific site(s) along the wound. Simple spotting of dressings from poorly approximated wound edges, small areas of ulceration, or marginal necrosis did not classify as persistent drainage.Patients with persistent postoperative wound drainage/clinical signs and symptoms of joint infection underwent open irrigation and debridement of their wounds with timing of the procedure related to the amount and persistence of clinical wound discharge. It was impossible for us to be more specific on this point. Clinical judgment was used to determine that these wounds could, very likely, not be expected to heal spontaneously.

Statistical analysis

A power analysis showed that 196 patients in each group were needed in order to detect a significant difference in the frequencies of major bleeding events between groups with 80% power and a confidence level of 95%. The Fisher exact test was used for the sample-size calculation with an estimated effect size of 4%. Demographics were compared to ensure that the

Table 1: Demographics features of cases enrolled in the study.

Male sex	90	78	
Female sex	60	72	
Female sex (%)	40	48	0.318
Mean age (yr)	49.08	48.26	0.340
Weight (kg)	65.39	63.83	0.063
Diagnosis of inflammatory arthritis (%)	20	26.67	0.400
Hip arthroplasty (%)	51.93	48.07	0.671
Knee arthroplasty (%)	47.06	52.94	0.480
Unilateral joint (%)	50.79	49.21	0.900
Bilateral joint (%)	48.62	51.38	0.900
General anesthesia	138	130	0.190
Regional anesthesia	12	20	0.190
Mean duration of surgery (min)	95.28	94.76	0.400
Mean intraoperative blood loss (ml)	351	358.33	0.653

Table 2: Major bleeding events in the two groups

Parameters	Group A (LMWH)	Group B (Aspirin + IPC)	P value
No. of patients with PRBC transfusion ≥2 units	29 (19.33%)	15 (10%)	0.033
No. of patients with mean Hb change ≥ 20 g/l	9 (6%)	4 (2.67%)	0.256
Hematoma requiring prolonged hospitalization	9 (6%)	1 (0.67%)	0.019
Hematoma requiring debridement	4 (2.67%)	0	0.122
Anemia with hypotension	3 (2%)	1 (0.67%)	0.622
Intracranial bleeding	0	0	
Epidural hematoma	0	0	
Retroperitoneal bleeding	0	0	
Gastrointestinal bleeding	0	0	
Urinary bleeding	0	0	
Myocardial Infarction	1	0	1
Heparin induced Thrombocytopenia	0	0	

randomization process had resulted in similar patient characteristics between groups. Chi-square tests were used to assess group differences in categorical variables, and independent t tests were used to compare continuous variables.

The Fisher exact test was used to compare the primary variable of safety, the frequency of major bleeding events, between the groups. Other bleeding data were compared between the groups as well. Categorical variables (the proportion of patients with a drop in the hemoglobin level of ≥20 g/L and the proportion of those who had a bleeding index of ≥2) were examined with use of the chi-square test. Continuous variables (the mean number of units of blood transfused and the mean bleeding index) were analyzed with use of independent t tests or the Mann-Whitney U test when appropriate. The secondary variable of efficacy, the frequency of venous thromboembolic events, was compared between groups by using a chi-square test. All tests were two-tailed, and the alpha level was set at 0.05.

Table 3: Minor bleeding events in the two groups

Paqrameters	Group A	Group B	P value
Bruises	47 (31.33%0	17 (11.33%)	0.001
Prolonged discharge	27 (18%)	7 (4.67%)	0.001
Cellulitis	16 (10.67%)	5 (3.33%)	0.0013

RESULTS

Of 300 patients enrolled from May 2010 to May 2012, 150 patients were enrolled in the low- molecular-weight heparin group (Group A) and 150 were in aspirin + intermittent pneumatic compression group (Group B). Not a single attrition was reported at the follow-up period of 3 months. Demographics were similar clinically in the two groups (Table 1).

A total of nine patients (6%) in group A and 1 (0.67%) in group B had major bleeding events and this difference was statistically significant (p=0.019) (Table 2). Total 47 patients (31.33%) in group A and 17 (11.33%) in group B had episodes of minor bleeding events, which was statistically significant (p=0.001). Though there were considerable differences between rates of major bleeding events, except for hematoma requiring prolonged hospitalization and PRBC units transfused, no finding was statistically significant (Table 4).

A total of 2 (0.67%) deep vein thrombi were detected by bilateral color Doppler study. Both the patients had popliteal vein thrombi, both were enrolled in group B (1.33%). No patient enrolled in group A had ultrasonography detected deep vein thrombosis (p=0.498). Both the patients had serial color Doppler done every 4 days, twice during their hospital discharge and were followed every 2 weeks. There was no propagation of thrombi and popliteal thrombi dissolved after 1 month in both the patients. No patients of either group had ultrasonography detected DVT after 6 week and 3 month follow up.

One (0.33%) patient had sudden onset dyspnea, tachypnea, tachycardia, and Pulmonary CT angiography proven pulmonary embolism (PE). The patient was enrolled in group B. The patient diagnosed with PE had normal color Doppler study of bilateral lower extremity. The patient was started on warfarin 5mg (eventually for period of 3 month) and enoxaparin 1mg/kg twice daily for period of 10 days. The patient was kept on Intensive care unit for period of 24 hours. There was no mortality from pulmonary embolism. Repeat color Doppler studies after 2 week, 6 week, and 3 month was normal.

DISCUSSION

In our prospective study involving 300 patients (409 joints) undergoing total hip and knee arthroplasty, we found the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in Indian population to be very low. Two (0.67%) patients out of 300 had popliteal vein thrombosis, one (0.33%) patient developed symptomatic pulmonary embolism, and none had fatal thromboembolic event. Both the patients with DVT and one patient with symptomatic PE were enrolled in group B. No patient enrolled in group A had any thromboembolic events. These results correspond favorably to those reported by Indian studies in the literature.[11-13]

We powered the study for an evaluation of safety instead of an assessment of efficacy for two reasons. First, practicing orthopedic surgeons are deeply concerned about bleeding issues associated with any of the utilized prophylactic drugs. This is demonstrated in the recent

American Academy of Orthopaedic Surgeons guidelines for prophylaxis against symptomatic pulmonary embolism following total hip arthroplasty.[1] [4]Second,clinically relevant thromboembolic events are so rare that statistically significant changes would be difficult to demonstrate. To show significance ($p<0.05$ at power 80%) in reducing the prevalence of PE 1% to 0.5%, would require more than 10,000 patients.[10]So the performance of a prospective,

Single center trial to assess pulmonary embolism-related death would require > 50,000 patients, making it a practical impossibility.

There have been changes in the clinical practice patterns that have contributed to the low incidence of thromboembolic events. Early mobilization is important. Most of our patients were out of bed on the second day of surgery. 89.33 percent patients received combined spinal epidural anesthesia, with good pain control with epidural analgesia, and belonged to ethnic group (Asian) who are anecdotally said to be at low risk for thromboembolic events.

Table 4. Comparison with the published literature.

Study	Procedure	Drug	Percentage
Fitzgerald et al[19]	TKA	LMWH	5.2
Colwell et al[20]	THA	LMWH	4
Shaieb et al[21]	THA-TKA	LMWH	3.3
Hull et al[22]	THA-TKA	LMWH	2.8
Leclerec et al[23]	THA-TKA	LMWH	2.1

The 0.6 percent prevalence of symptomatic, nonfatal pulmonary embolism compares favorably with the rates of 0.7 percent for patients managed with low-molecular- weight heparin (in a meta-analysis of 2065 patients in twenty studies[15]) and 2.7 percent for those managed with warfarin (in meta-analysis of 864 patients in ten studies[15]).

Literatures comparing LMWH and compression device plus aspirin were very rare.[16-18]

Our findings with regard to venous thromboembolic events support those in a previously reported study comparing a compression device plus aspirin with low-molecular-weight heparin.[16]In that study, Clifford et al[16]found rate of major bleeding events was 0% in the compression group and 6% in the low-molecular-weight heparin group. The rates of distal and proximal deep venous thrombosis were 3% and 2%, respectively, in the compression group compared with 3% and 1% in the heparin group. The rates of pulmonary embolism were 1% in the compression group and 1% in the heparin group, and there were no fatal pulmonary emboli.

In our study, the risks of major bleeding events (0.671 percent) and minor bleedings events (11.33%) with the use aspirin plus intermittent pneumatic compression devices were substantially lower than 6 percent risk of major bleeding events and 31.33 percent risk of minor bleeding events with LMWH use in our study and those reported in literature (Table 4).

The need for extended thromboprophylaxis beyond the current routine three to four-day hospital stay following total hip arthroplasty has been well documented in the literature.[24-26]

Use of 325 mg aspirin twice a day for period of 6 weeks in compression group has huge advantage over in-patient LMWH protocol.

In our study subsequent color Doppler studies in 6 week and 3 month follow up had no incidence of thromboembolic events. This finding suggests that the asymptomatic deep-vein thromboses that were detected on the postoperative duplex scans had most likely developed intraoperatively or in the early postoperative period.

Our study was limited because the number of patients was not adequate to delineate the difference in efficacy between the two methods of prophylaxis. The lack of blinding in this study is also a limitation, although compression-device studies are difficult to blind.

CONCLUSIONS

The incidence of thromboembolic events in Indian patients undergoing knee and hip arthroplasty is low. The risk of deep vein thrombosis (DVT) in our study was 0.67%, that of symptomatic pulmonary embolism (PE) 0.33%, and 0% for fatal thromboembolic events.

Our data suggest that an inexpensive multimodal protocol, consisting of aspirin, exercises, and the use of intermittent compression devices, was associated with few thromboembolic complications.

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