



Efficacy and safety of Aspirin plus intermittent pneumatic compression device as thromboprophylaxis after total hip arthroplasty : prospective randomized control trial

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Total hip arthroplasty is extremely successful orthopedics procedure that relieves pain, improve function, and enhance the quality of patient's lives. However, this procedure is not without complications, the most notable being the risk of morbidity and mortality from the venous thromboembolic events. The purpose of this study was to find out the incidences of deep vein thrombosis and pulmonary embolism in Indian patients undergoing total hip joint arthroplasty and compare effectiveness and safety of thromboprophylaxis with aspirin plus intermittent pneumatic compression device with that of low molecular weight heparin.

Patients who had total hip arthroplasty (unilateral/bilateral) were randomized to receive prophylaxis with aspirin plus intermittent pneumatic compression device or low molecular weight heparin. After four to six days, all patients underwent bilateral lower-extremity color doppler ultrasonography to screen for deep venous thrombi in the calf, thigh, and pelvic veins. Any clinical symptoms of pulmonary embolism were evaluated clinically by cardiologist and confirmed with pulmonary CT angiography. Bleeding events in both groups were documented. The patients were followed up at 6 week and 3 month with color doppler to look for the evidence of deep venous thrombi.

180 patients (224) joints) were randomized into 2 groups and studied regarding the incidence of deep vein thrombosis and pulmonary embolism and safety and efficacy of the drugs used as thromboprophylaxis. Demographics were similar clinically between

the groups. Prevalence of deep vein thrombosis and pulmonary embolism in Indian patients who underwent total hip arthroplasty was 1.11% and 0.55% respectively. The rates of deep venous thrombosis were 2.22%, in the aspirin plus compression group compared 0% in the low molecular weight heparin group. The rates of pulmonary embolism were 1.11% in the Aspirin plus compression group and 0% in the heparin group, and there were no fatal pulmonary emboli. Within the six weeks and three months follow-up, no thromboembolic events occurred. The rate of major bleeding events was 1.11% in the aspirin and compression group and 10% in the low-molecular-weight heparin group.

An inexpensive multimodal protocol, consisting of aspirin, exercises, and the use of intermittent compression devices, was associated with few thromboembolic complications.

When compared with low-molecular-weight heparin, use of the aspirin plus intermittent pneumatic compression device for prophylaxis against venous thromboembolic events following total hip arthro-

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plasty resulted in a significant decrease in major bleeding events.

Keywords: Aspirin, Deep vein thrombosis, Low molecular weight heparin, Pulmonary embolism, Total hip arthroplasty

Level of Evidence: Therapeutic Level I

INTRODUCTION

Total hip arthroplasty (THA) is one of most successful procedures of the modern orthopedics that relieve pain, improve function, and enhance the quality of patient's lives. However, this procedure is associated with dreaded complication of venous thromboembolic events (11). Venous thromboembolism may present as distal deep vein thrombosis (DVT), proximal DVT, and pulmonary embolism (PE), the last of which in some cases can be fatal (17). The reported incidence of distal vein thrombosis after THA without prophylaxis is 40%-70%, proximal DVT 10%-20%, clinical DVT 1%-3%, non-fatal symptomatic pulmonary thromboembolism 1%-2%, and fatal pulmonary thromboembolism 0.1%-1% respectively (9,16). Johnson et al. in a series of 7959 total hip replacements performed between 1962 and 1973 reported that the overall prevalence of pulmonary embolism was 7.89 percent and that of fatal pulmonary embolism was 1.04 percent (12). Similarly, in 1974, Coventry et al. reported an overall prevalence of pulmonary embolism of 2.2 percent in a series of 2012 consecutive total hip replacements. In a subset of 62 patients who had received no prophylactic anticoagulation, the prevalence of fatal pulmonary embolism was 3.4 percent (6).

Dorr et al. retrospectively reviewed the records on 1179 consecutive total joint arthroplasties in 970 patients who had undergone primary and revision total hip and total knee replacement (14). 856 patients (1046 operations) were considered to be low risk and were managed with aspirin, dipyridamole, or clopidogrel bisulfate as well as intermittent pneumatic calf compression devices. 144 pts (133 operations) were considered to be high risk and managed with low molecular-weight heparin or

warfarin and intermittent calf compression. No fatal pulmonary embolus was detected. 3 nonfatal pulmonary emboli (prevalence, 0.3 percent) were detected in association with the 1046 procedures in the low risk group, and none were detected in association with the 133 operations in the high-risk group ($p = 0.767$). Symptomatic deep venous thrombosis was detected in 4 (0.38 percent) of the 1046 operations in the low-risk group and 1 (0.75%) of the 133 operations in the high-risk group ($p = 0.93$).

Chemical prophylactic agents such as aspirin, warfarin, heparin, and pentasaccharides, as well as physical modalities such as compression stockings and lower extremity pumps are used to minimize the risk of VTE (2).

The widespread belief that the rate of fatal pulmonary embolism after total hip replacement arthroplasty is more than 1% is based on the findings of few studies conducted mainly in the 1960s and 1970s (19,20). During the last decade, the incidence of fatal PE has decreased substantially to a rate of 0% to 0.2% (19,20). 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. This incidence appears to be consistent no matter which prophylactic agents are used (20).

Among Asians, particularly Indian population, it has been said anecdotally that there is a considerably lower prevalence of deep vein thrombosis (24,25). 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 (the results of which are also controversial) may not be justifiable.

MATERIALS AND METHODS

The study was prospective randomized controlled trial conducted in the Department of orthopedics, at a tertiary care referral centre. 180 patients (224 joints) were enrolled after informed and written

consent and prospectively followed and studied from May 2010 to May 2012. Prior approval for the study was obtained from the Institutional Ethics Committee.

All the patients who were scheduled for unilateral or bilateral total hip arthroplasty 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 blinded to the type of intervention. All the eligible patients were randomized either to receive enoxaparin 40mg once a day s/c 12 hours 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.

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 (intracerebral, intraocular, intraspinal, 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 $\geq 2 \times 2$ 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

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 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.

RESULTS

Of 180 patients enrolled from May 2010 to May 2012, 90 patients were enrolled in the low- molecular-weight heparin group (Group A) and 90 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).

9 patients (10%) in group A and 1 (1.11%) in group B had major bleeding events and this difference was statistically significant ($p=0.019$) (Table 2).

47 patients (52.22%) in group A and 17 (18.89%) 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 3).

A total of 2 (1.11%) deep vein thrombi were detected by bilateral color Doppler study. Both the patients had popliteal vein thrombi, both were enrolled in group B (2.22%). No patient enrolled in group A had ultrasonography detected deep vein thrombosis ($p=0.498$). Both were treated with warfarin 5mg and enoxaparin 1mg/kg twice daily, dosage titrated to achieve target INR 2. 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 (0.56%) 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 180 patients (224 joints) undergoing total hip, we found the

Table I. — Demographics features of cases enrolled in the study

	Group A (N=90)	Group B (N=90)	Range	P value
Male sex	51	48		
Female sex	39	42		
Mean age (yr)	49.08	48.26	19-85	0.340
Weight (kg)	65.39	63.83	45-110	0.063
Diagnosis of inflammatory arthritis (%)	20	26.67		0.400
Unilateral joint (%)	61.20	59.63		0.403
Bilateral joint (%)	37.93	40.37		0.606
Regional anesthesia	83	81		0.637
General anesthesia	7	9		0.637
Mean duration of surgery (min)	95.28	94.76	45-190	0.400
Mean intraoperative blood loss (ml)	351	358.33	150-700	0.653

Table II. — Major bleeding events in the two groups

	Group A (LMWH)	Group B (Aspirin + IPC)	P value
No. of patients with PRBC transfusion \geq 2 units	29 (32.22%)	15 (16.67%)	0.033
No. of patients with mean Hb change \geq 20 g/l	9 (10%)	4 (4.44%)	0.256
Hematoma requiring prolonged hospitalization	9 (10%)	1 (1.11%)	0.019
Hematoma requiring debridement	4 (4.44%)	0	0.122
Anemia with hypotension	3 (3.33%)	1 (1.11%)	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	

Table III. — Minor bleeding events in the two groups

	Group A	Group B	P value
Bruises	47 (52.22%)	17 (18.89%)	0.001
Prolonged discharge	27 (30%)	7 (7.78%)	0.001
Cellulitis	16 (17.78%)	5 (5.56%)	0.0013

incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in Indian population to be very low. Two (1.11%) patients out of 180 patients had popliteal vein thrombosis, one (0.55%) 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). 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 (20). 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 (20).

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. 92.22 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.

The 1.11 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) and 2.7 percent for those managed with warfarin (in meta-analysis of 864 patients in ten studies) (13).

Literatures comparing LMWH and compression device plus aspirin were very rare (3,8,18,25).

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 (3). In that study, Clifford et al. (3) 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 (1.11%) and minor bleedings events (18.89%) with the use aspirin plus intermittent pneumatic compression devices were substantially lower than 10 percent risk of major bleeding events and 52.22 percent risk of minor bleeding events with LMWH use in our study and those reported in literature.

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 (4,7,21).

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.

CONCLUSIONS

The incidence of thromboembolic events in Indian patients undergoing hip arthroplasty is substantially lower than their western counterparts. Also, significant is the fact that the global threat of thromboembolic events after total joint arthroplasty has been substantially reduced during the past decade. The risk of deep vein thrombosis (DVT) in our study is 1.11%, that of symptomatic pulmonary embolism (PE) 0.56%, and 0% for fatal thromboembolic events. The worldwide risk of fatal pulmonary embolism is 0.1%. This reduction in risk is due to confluence of changes in our medical practices including early mobilization, more efficient and less traumatic surgical procedures, better pain management, and use of regional anesthesia.

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.

Our study does not allow us to state that the administration of aspirin and compression device was totally responsible for the low rate of thromboembolic complications. It is likely that the use of regional anesthesia, the less traumatic surgery, and an intensive intraoperative and postoperative program of physical exercises were also important features.

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