Original Article

Comparative study of extended versus short term thromboprophylaxis in patients undergoing elective total hip and knee arthroplasty in Indian population

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Abstract

Background: Postoperative thromboprophylaxis with low molecular weight heparin (LMWH) for an extended period of 4 weeks is now preferred over short term thromboprophylaxis in patients undergoing total hip/knee arthroplasty (THA/TKA). However, most of the data demonstrating the efficacy and safety of extended thromboprophylaxis and short term thromboprophylaxis is from clinical trials done in the West. In India, the data of the incidence of venous thromboembolism (VTE) following THA/TKA has been conflicting and the duration has not been clearly defined. The aim of the study was to evaluate and compare the efficacy of extended thromboprophylaxis over short term thromboprophylaxis in Indian patients undergoing elective THA/TKA surgeries.

Materials and Methods: A prospective arm of 197 consecutive patients undergoing elective THA/TKA surgeries who were administered extended thromboprophylaxis for 4 weeks was compared with a historical group of 795 patients who were administered short term thromboprophylaxis for only 7-11 days. In both groups, LMWH (enoxaparin) was used in a dose of 40 mg subcutaneously, in addition to mechanical thromboprophylaxis. Primary efficacy endpoint was objectively confirmed venous thromboembolism (VTE). The presence of DVT was confirmed by a combination of pretest scoring, D-dimer, and Color Doppler Flow Imaging (CDFI) of deep veins of the legs, and pulmonary thromboembolism (PTE) was confirmed by ventilation perfusion (V/Q) scan or pulmonary angiography. Fisher's exact test and *t* test were used for the statistical analysis. The baseline confounding factors were compared between the two groups using *t* test for comparing the means for continuous data and Fisher's exact test for categorical data.

Results: In the prospective arm, only 1 patient developed symptomatic PTE compared to 26 (3.27%) cases of VTE (20 cases of PTE and 6 cases of DVT) in the retrospective group.

Conclusion: Extended thromboprophylaxis (for 4 weeks) was found to be more effective than short term thromboprophylaxis in minimizing the risk of postoperative VTE in patients who underwent THA/TKA.

Key words: Deep vein thromboembolism, LMWH, pulmonary embolism, thromboprophylaxis, venous thromboembolism

Introduction

Venous thromboembolic complications are common in patients who undergo total hip or knee arthroplasty (THA/TKA) without thromboprophylaxis.[1,2] The incidence of symptomatic venous thromboembolism (VTE) is around 3-7%,[1,2] whereas it rises to about 40-70% in various studies when screened for asymptomatic VTE in addition to symptomatic VTE. Hence, some form of thromboprophylaxis is indicated for the prevention of VTE. VTE includes both deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE). The term thromboprophylaxis includes both mechanical and pharmacological modalities. One of the best options is low molecular weight heparin (LMWH), which is also cost effective.[1-3] It has also been observed that the risk for VTE is more protracted after hip/knee arthroplasty surgeries due to peculiarities in surgical technique and hemodynamics.[3] Data from the West has demonstrated that prolonged thromboprophylaxis (4 weeks) has significantly reduced the morbidity and mortality from VTE in patients undergoing THA/TKA.[3-9] However, in India, the actual incidence of VTE is not known and the duration of thromboprophylaxis has not been clearly defined in postoperative situations such as THA/TKA. The Indian data regarding the incidence

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of VTE and duration of thromboprophylaxis has been heterogeneous and conflicting.[10-13] Therefore, it was necessary to establish the exact incidence of VTE (both asymptomatic and symptomatic) in a representative sample of multiethnic Indian patients undergoing THA/TKA. The aim of the study was to evaluate and compare the efficacy of extended thromboprophylaxis over short term thromboprophylaxis in Indian patients undergoing elective THA/TKA surgeries.

Materials and Methods

A combined prospective and retrospective nonrandomized, observational study was conducted in a cohort of 992 multiethnic Indian patients, who underwent THA/TKA. Patients undergoing primary elective THA/TKA were included in the study if they were > 18 years old and weighing 45-95 Kg. Patients who were excluded from the study have been enumerated in Table 1.

A prospective arm of 197 consecutive patients who were administered extended thromboprophylaxis of 4 weeks with enoxaparin 40 mg subcutaneously (SC) daily was compared with a retrospective group of 795 patients from the hospital registry, who were operated for primary THA/TKA during the period 1998-2004 and were administered short term thromboprophylaxis with enoxaparin (Clexane, AventisR) for a period of 7-11 days (average 9 days).

Primary efficacy endpoint was objectively confirmed VTE. The presence of DVT was confirmed by a combination of pretest scoring, D-dimer, and Color Doppler Flow Imaging (CDFI) of deep veins of the legs. PTE was confirmed by ventilation perfusion (V/Q) scan or pulmonary angiography (PA). The detailed study protocol is illustrated in Figure 1. This study was conducted by the Department of Clinical Haematology, with the Joint Replacement Centre, at a tertiary care hospital from Jan 1998 to Dec 2008. This hospital caters for referred defense service personnel and their dependent family members who form a representative sample of the multiethnic Indian population [Figure 2]. All good clinical practice guidelines were observed and the hospital research medical subcommittee approved the study.

The benefits and risks involved were discussed with the patient and informed consent was taken. The patients who fulfilled the above criteria were included in the study. A detailed history was recorded with reference to name, age, sex, address, any predisposing factors, medication, and past medical/surgical history. All the patients were subjected to a detailed physical and clinical examination, and a pretest scoring for DVT as per the Well's risk stratification score were assigned for each patient.[14] A score of 2 or more indicates a likely probability of DVT; a score of less than 2 indicates that DVT is unlikely.

Blood samples were collected in vacutainer tubes and a

Table 1: Details of the excluded patients in the prospective arm

Details of patients excluded*	Number of patients (*n*)
Antiplatelet drug/oral anticoagulant within the week preceding inclusion	66
Hemostasis was not achieved within 24 h after surgery	12
THA/TKA on one limb was performed within one month	80
History of documented VTE in last 6 months	06
Acute DVT	02
Deranged LFT with PT/INR abnormalities	04
Thrombocytopenia	32
Documented MI/stroke within 1 month	03
Peptic ulcer disease, ulcerative dyspepsia, IBD	05, 10, 03
Did not give informed consent	42
Documented allergy/skin rash/necrosis with the use of LMWH	Nil

*Some patients had more than one reason for exclusion and were counted in either criteria.
Abbreviations: THA = Total hip arthroplasty, TKA = Total knee arthroplasty, VTE = Venous thromboembolism, DVT = Deep vein thrombosis, LFT = Liver function test, PT = Prothrmobin time, INR = International normalised ratio, MI = Myocardial infarction, IBD = Inflammatory bowel disease, LMWH = Low molecular weight heparin

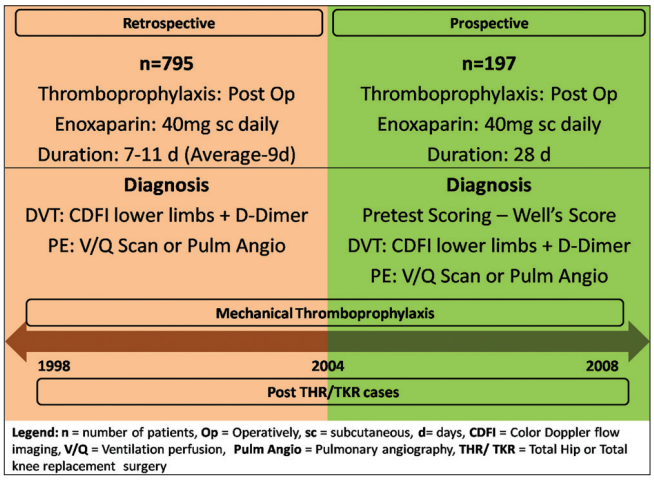

Figure 1: Study protocol

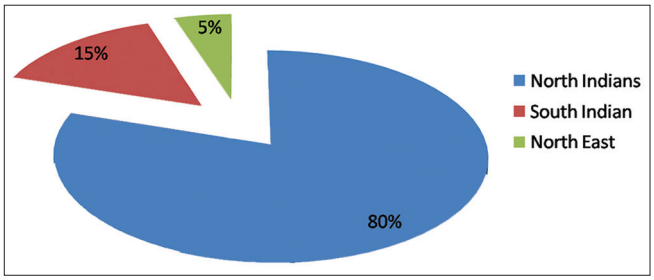

Figure 2: Demographics of prospective group

baseline hemogram [hemoglobin (Hb), total leukocyte count (TLC), differential leukocyte count (DLC), platelets], coagulogram [prothrombin (PT) and partial thromboplastin time with kaolin (PTTK)], and biochemistry [blood urea nitrogen (BUN), creatinine, electrolytes, and blood sugar] were done in all patients.

All patients in the prospective arm (n = 197) were given enoxaparin (Clexane, Aventis®) 40 mg SC OD by a qualified nurse, starting 12 h (range 10-14 h) preoperatively administered over the lateral aspect of the anterior abdominal wall. Only one brand of LMWH was used during the study as the method of preparation, half-life, pharmacokinetics, and bioavailability are different for different preparations and the results of one cannot be extrapolated to the other. Patients/relatives were taught how to administer the injections during the hospital stay and were given a handout regarding the necessary precautions to be taken. No patient remained immobilized beyond 72 h and a strict mobilization protocol was followed for both the prospective and retrospective groups. The postoperative protocol in our hospital includes drain removal and patient made to stand up and sit on bedside; and carry out quadriceps contraction exercises in extension, ankle exercises, 90° flexion, and assisted extension at the operation site, 48 h postoperatively. Patient was mobilized to toilet and back by 3rd to 7th postoperative day and discharged by 10th to 14thday. For 6 weeks postoperatively, they were advised assistance with a stick/elbow crutch (in opposite hand for THR, same hand in unilateral TKR, and dominant hand in bilateral TKR). This protocol was common for both prospective and retrospective groups [Figure 3]. Thromboprophylaxis was given for 28 days in the prospective arm, while it was discontinued in the retrospective arm at the time of discharge.

Mechanical measures for thromboprophylaxis in the form of venous foot pumps (preambulatory) and graduated compression stockings (postambulatory) were used in all patients of both groups as part of the standard hospital practice (thus eliminating any confounding effect on the outcomes). In our study, we noted the benefits of thromboprophylaxis with enoxaparin in both the groups over and above the mechanical thromboprophylaxis. Postoperatively, the patients were followed up weekly for 4 weeks to rule out DVT or the occurrence of PTE.

All patients underwent D-dimer tests at baseline, 7-11 days, and 28 days postoperatively. D-dimer testing was done with latex agglutination slide test (using D-DI® test

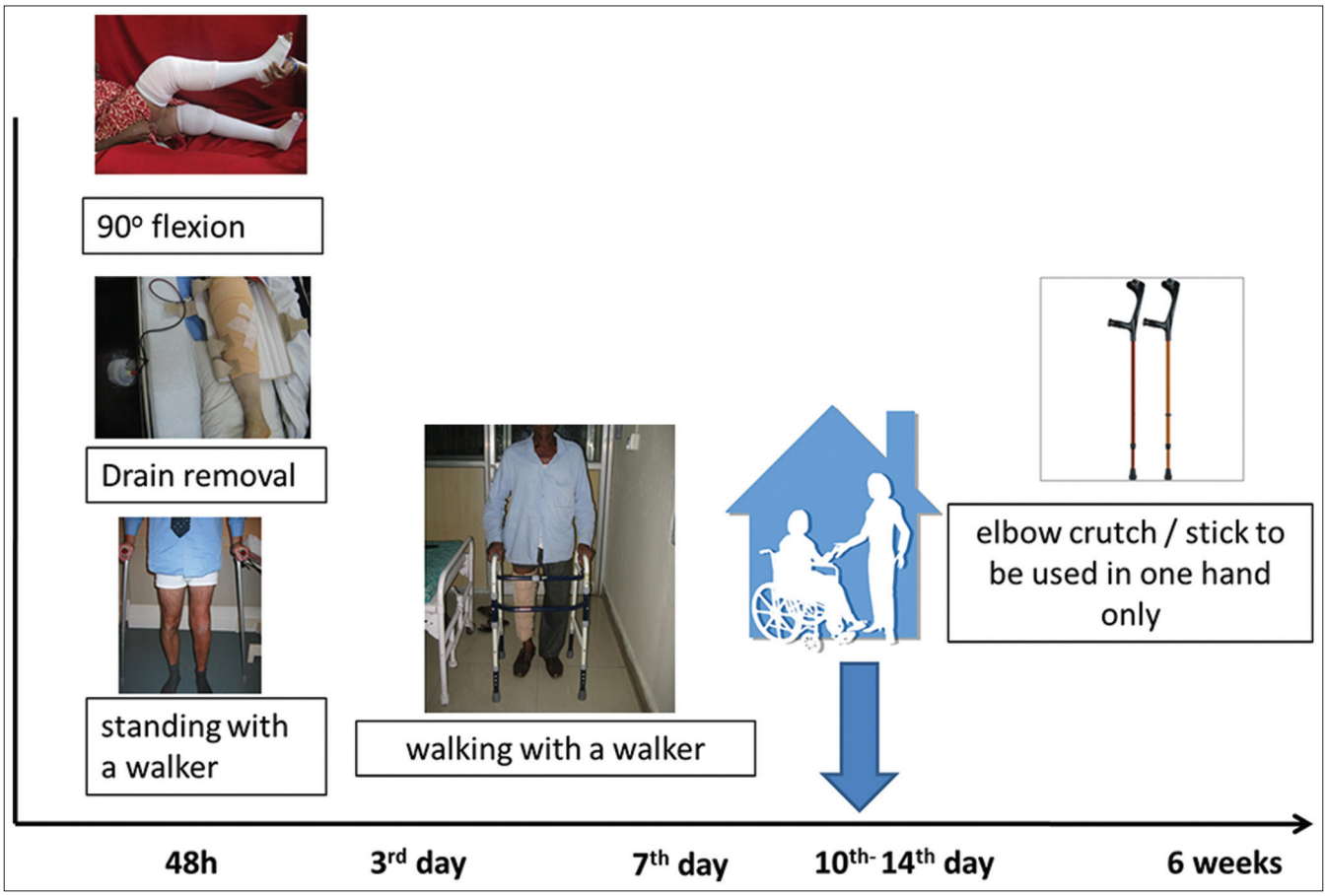

Figure 3: Mobilization protocol

kit) in the laboratory according to the manufacturer›s specifications. The latex particles provided in the D-DI test were coated with mouse monoclonal antibodies. Test samples containing D-dimers when mixed with latex particle suspension resulted in particle agglutination. The D-DI test was designed to have a positive cutoff at ≥0.5 mcg/ml expressed in fibrinogen equivalent units.

CDFI of the deep veins of lower limbs was done in all patients on day 0 (baseline), 7-11 days, and day 28 postoperatively using a GE LOGIQ 460 MD Color Doppler®. A 7.5 MHz probe was used for visualization of larger veins of the leg, while a 3.5 MHz probe was used for smaller veins. In acute thrombosis (less than 10 days old), the vein viewed in transverse section was noted to be distended more than twice the size of the accompanying artery. As the age of the thrombus increased, the vein became smaller than the artery due to clot organization and retraction. Because many thrombi did not completely obstruct the lumen and permitted some residual flow near the vein wall, the critical criterion used was the inability to compress the vein completely. In the case of clinically suspected PTE, V/Q lung scanning or PA was performed.

All instances of postoperative hemorrhage, wound hematoma, and reexploration were recorded. Hemorrhages were classified as minor or major. "Major hemorrhage" was defined as clinically overt bleeding that was associated with a decrease in the hemoglobin level of 2 g/dL or more; requiring transfusion of two or more units of red blood cells; bleeding that was retroperitoneal or intracranial in location; or bleeding that necessitated reexploration. The hemorrhage was defined as minor if it was overt but did not meet the criteria for major hemorrhage, and was associated with at least one of the following features: Epistaxis lasting more than 5 min or requiring intervention; ecchymosis or hematoma larger than 5 cm at its greatest dimension; hematuria not associated with urinary catheter related trauma, gastrointestinal hemorrhage not related to intubation or placement of a nasogastric tube; wound hematoma; subconjunctival hemorrhage or complications necessitating cessation of LMWH. Patients were also assessed for other side effects such as heparin-induced thrombocytopenia, local irritation, and allergy.

The baseline confounding factors were compared between the two groups using *t* test for comparing means for continuous data and Fisher's exact test for categorical data. The comparison of occurrence of primary outcome between two groups was done by Odds Ratio. The side effect profile of LMWH was compared with Fisher's exact test. The significance level for the above tests was set to be 0.05.

Results

Analyses were performed to determine the incidence of VTE following unilateral/bilateral hip/knee arthroplasty and study the safety profile of this protocol.

The mean age of patients at the time of presentation was 58.3 ± 15.7 years (range 18-85 years) [Table 2]. Young patients (<20 years) constituted around 4% of our study population, the youngest being 18 years of age, a case of sickle cell disease with avascular necrosis (AVN) hip who was subjected to THR. The mean weight was 65.7 ± 10.2 kg (range 48-92 kg). Over half the patients (107/197 (54.3%)) were females. A total of 86 patients (43.6%) underwent THR (bilateral 81/197 (41%) and unilateral 5/197 (2.5%)), while the rest underwent TKR (bilateral 64/197 (32.4%) and unilateral 47/197 (23.8%)). Combined general anesthesia (GA) and epidural anaesthesia was administered to 68 patients (34.5%), GA alone to 61 patients (31%), spinal epidural anesthesia to 53 patients (26.9%), and 15 patients (7.6%) were subjected to subarachnoid block. The main comorbidities were hypertension alone in 40 cases (20.3%), diabetes mellitus in 24 (12.2%), coronary artery disease in 13 (6.59%), hypertension and diabetes mellitus in 21 (10.7%), and hypertension and coronary artery disease in 11 (5.6%). The baseline characteristics in prospective arm were comparable with those of the retrospective arm, with the differences being statistically insignificant [Table 2].

Every patient was subjected to a clinical examination at baseline, 7-11 days, and on 28th day. Only three patients were detected to have likelihood of DVT with a pretest score of 2 at 7-10 days. However, further evaluation with D-dimer and CDFI ruled out DVT in these patients.

The mean baseline Hb was 12.57 ± 1.63 g/dl (range 8.2-16.4 g/dl); on day 8-10 it was 11.39 ± 1.64 g/dl (range 7.4-14.6 g/dl), while on day 28 it was 12.03 ± 0.95 g/dl (range 8.6-14.8 g/dl). TLC, DLC, and platelet counts at baseline, day 8-10, and day 28 were within normal limits. Coagulation parameters monitored preoperatively and postoperatively were found to be within normal limits in all patients. The baseline D-dimer values were normal (<0.5 mcg/ml). The two groups were compared for the confounding factors as depicted in Table 2. The two groups were comparable in the possible confounding factors.

Of the 197 patients in the prospective arm, only one patient had VTE (0.5%), whereas 26 out of 795 patients (3.27%) in the retrospective arm had VTE. Twenty one patients (one of these belonged to prospective arm) had positive V/Q scan and 6 had negative V/Q scan results [Table 3]. Out of 26 patients who were found to have VTE in the

Table 2: Baseline patient characteristics

Demographics	Prospective patients (*n*=197) (%)	Retrospective patients (*n*=795) (%)	Statistical test for comparison	*P* value
Age (years)	58.3	57.4	*t* test	0.67
Sex (males)	90 (45.7)	378 (47.6)	Fisher's test	0.74
BMI (kg/m^2)	26.3	25.2	*t* test	0.35
Nicotine intake	34 (17.25)	135 (17)	Fisher's test	0.23
Diabetes mellitus	24 (12.2)	117 (14.7)	Fisher's test	0.13
CAD	13 (6.59)	48 (6.06)	Fisher's test	0.16
Hemoglobin (g/dl)	12.6	13.8	*t* test	0.35
TLC (per μl)	8200	7300	*t* test	0.23
Platelets (per μl)	242,000	234,000	*t* test	0.31
PT (INR)	1.23	1.34	*t* test	0.22
aPTT (sec)	32	36	*t* test	0.13
Site of replacement				
Knee	111 (56.3)	496 (62.4)	Fisher's test	0.14
Hip	86 (43.7)	299 (37.6)		0.14
Unilateral vs. bilateral replacement				
Unilateral	52 (26.4)	196 (24.65)	Fisher's test	0.23
Bilateral	145 (73.6)	599 (75.35)		0.23
Duration of hospitalization (days)	14.6	15.9	*t* test	0.24

Table 3: Primary outcome-incidence of VTE

Outcome	Prospective (*n*=197)					Retrospective (*n*=795)				
	Hip		Knee		Total	Hip		Knee		Total
	Unilateral	Bilateral	Unilateral	Bilateral		Unilateral	Bilateral	Unilateral	Bilateral	
DVT	00	00	00	00	00	04	00	02	00	06
PTE	00	00	00	01	01	07	00	11	02	20
VTE	00	00	00	01	01 (0.5%)	11	00	13	02	26 (3.27%)

Odds Ratio = 0.15 (95% Confidence Interval = 0.03-0.86) *P* value; DVT = Deep vein thrombosis; PTE = Pulmonary thromboembolism; VTE Venous thromboembolism

Table 4: Evaluation of safety profile

Complications*	Prospective group (*n*=197)					Retrospective group (*n*=795)					Statistical test
	Hip		Knee		Total	Hip		Knee		Total	Fisher exact test
	Unilateral	Bilateral	Unilateral	Bilateral		Unilateral	Bilateral	Unilateral	Bilateral		*P* value
Hemorrhage (major)	Nil	01	Nil	03	04	02	03	02	08	15	0.77
Hemorrhage (minor)	02	09	05	10	26	09	30	18	46	103	0.90
Thrombocytopenia	01	Nil	01	02	04	02	05	02	06	15	0.77
Pruritis	03	04	03	02	12	10	14	10	12	46	0.86

*Deaths = Nil

retrospective arm, 6 patients had DVT (5 were distal and 1 was proximal) and 20 cases had PTE. Of these 26 VTE cases, 13 underwent unilateral TKR, 11 unilateral THR, and 2 cases underwent bilateral TKR. No VTE was noted in bilateral THR cases. The reduction in the frequency of VTE with extended enoxaparin treatment was statistically significant ($P = 0.018$). In the retrospective arm, 26 cases developed VTE, 6 in the first week, 1 in 8-14 days, 2 cases in 15-21 days, and 17 cases in 21-28 days. In the prospective arm, only one patient developed VTE (as PTE) between 21 and 28 days.

Bleeding episodes in the prospective arm ($n = 197$) included 4 cases (2%) of major bleeding episodes requiring repeat surgery and 26 (13.2%) cases of minor bleeds in the form of local hematoma over the injection site and epistaxis. In the retrospective arm, 15 cases (1.88%) had major hemorrhage and 103 patients (12.95%) had minor bleeds. Local irritation in the form of pruritis was seen in 12 patients (6.1%) who used prolonged LMWH, whereas 46 patients (5.78%) in the retrospective group had local irritation, which responded to symptomatic treatment. Hence, the incidence of major/minor bleeds and local irritation was comparable in the two groups [Table 4].

There was no case of heparin-induced thrombocytopenia. However, mild (<50% fall from baseline levels) transient thrombocytopenia occurred in 4 patients (2.03%) in the prospective group and in 15 patients (1.88%) in historical control group which recovered spontaneously. Type of surgery and type of anesthesia had no impact on the outcome.

Discussion

To the best of our knowledge, our study is the first of its kind from the Indian subcontinent to compare the efficacy of extended thromboprophylaxis for 28 days using LMWH (enoxaparin) with that of short term thromboprophylaxis for 7-11 days.

In contrast to the trials where invasive phlebography was used for confirmation of the diagnosis of DVT, we used a combination of noninvasive investigations including pretest scoring, CDFI of deep veins of lower limbs, and D-dimer. Various studies have shown that CDFI is a viable alternative to contrast venography, as the latter is considered the gold standard for the diagnosis of DVT.[15,16] Incorporating D-dimer testing based on clinical pretest probability and CDFI testing provided a simplified and safe diagnostic strategy for the evaluation of patients.[14,17]

In our study, enoxaparin (Clexane, Aventis) was used for thromboprophylaxis in all patients who underwent THA/TKA. It was well tolerated and safe. In keeping with previous observations, we did not observe any bleeding complications during spinal anesthesia in patients receiving enoxaparin. The incidences of major and minor bleeds in the two groups were comparable with those reported in existing literature.

Extended thromboprophylaxis with LMWH showed consistent effectiveness and safety among various clinical trials in the West.[3-9] These findings support the need for extended thromboprophylaxis in patients undergoing THA/TKA. However, the Asian and Indian data have been conflicting. As per one study conducted in 2004, the incidence of DVT without thromboprophylaxis after THR (n = 45) and TKR (n = 26) in Indian patients has been low (4.4% for THR and 0% for TKR).[10] Another study of 147 patients without thromboprophylaxis following total hip arthroplasty (THA) (n = 23), total knee arthroplasty (TKA) (n = 22), and proximal femur fracture fixation PFF (n = 102) revealed DVT in 6.12% and PTE in 0.6% of patients.[11] However, a few studies revealed relatively higher incidence of VTE. In a randomized control trial conducted in 2003, Agarwala *et al*. found the incidence of DVT in Indian patients who had undergone THA/TKA without any thromboprophylaxis to be 60% (screening by venography), while those who received thromboprophylaxis reported a 43.2% incidence of DVT.[12] However, these patients received only short term thromboprophylaxis of 7 days. Another study revealed the incidence of venographic thrombosis after major joint surgery in Asian patients without thromboprophylaxis at 41%.[13] Both the studies mentioned above used contrast venography to detect VTE. High rates of VTE may be due to inadequate dose of LMWH (2500 IU against the standard doses of 4000 IU), though the exact nature of molecule used is not mentioned. Also, these patients received only short term thromboprophylaxis of 7 days. These variations could also be due to the study design and ethnic differences of patients treated in various regional centers in India.

In our study, the incidence of VTE was 0.5% in the prospective arm, while it was 3.27% in the retrospective arm of patients in whom short term thromboprophylaxis was given. In the retrospective group of patients, no screening for asymptomatic DVT was done; hence, the actual incidence of VTE could have been higher than noted. In contrast to other studies from India, the patients in our study group were representative of the Indian population as they belonged to different ethnic and cultural groups.

The main outcome was the significant reduction in the incidence of VTE (0.5% vs. 3.27%) in patients administered extended thromboprophylaxis for 4 weeks (compared to 7-11 days in the retrospective control group) in a multiethnic, representative cohort of Indian patients undergoing elective THA/TKA. Extended thromboprophylaxis was also found to be safe in the context of major and minor bleeding manifestation. This benefit of extended thromboprophylaxis is in keeping with published data from the West. Since the risk of thrombosis is present over a 6-8 weeks period, being highest in the first few weeks, many centers have extended the period of thromboprophylaxis to even 6 weeks. Even in the retrospective control group incidence of symptomatic VTE is lower (3.27%) in Indian patients who received thromboprophylaxis for 7-11 days as compared to the much higher incidence noted amongst Caucasian patients. This regimen was also found to be safe with no major adverse events. Though it is not a major outcome of the study, it is an additional observation which could translate into future study by itself.

Though we found a significant reduction in the rates of VTE with extended thromboprophylaxis, this trend needs to be confirmed in a larger cohort of patients. Though our study is one of the largest in India, it is still underpowered to make definitive recommendations. Other limitations include the use of retrospective control group, which by definition becomes uncontrolled in terms of intervention/evaluation. Also, this group was not evaluated for asymptomatic DVT postoperatively. Preoperative duplex scanning for asymptomatic DVT, though debatable,[15] was not done in our study. The hospital has a thorough workup plan and follows strict standard operating procedures and has good record maintenance, thus facilitating analysis of laid down variables in this study for the retrospective group. Since it has been established beyond doubt in western

literature that extended thromboprophylaxis of four or more weeks is distinctly superior to placebo, we thought it to be "unethical" to subject a prospective cohort to short term thromboprophylaxis, hence historical controls were used. However, the strengths of our study include a reasonably large cohort, a multiethnic population, and use of a single brand of heparin for all patients.

To conclude, the extended thromboprophylaxis was found to be more effective than short term thromboprophylaxis when used in multiethnic Indian patients without compromising the safety of the patients. As the overall incidence of the VTE is low in Indian patients even with short term thromboprophylaxis, further studies are warranted to evaluate the genetic and environmental factors.

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