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Original Article

Thromboembolic disease after knee arthroplasty is rare in Southern Iran

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ARTICLE INFO

Article history:

Received 1 November 2013

Accepted 5 January 2014

Available online 31 January 2014

Keywords:

Venous thromboembolism

Warfarin

Enoxaparin

Total knee replacement

Iran

ABSTRACT

Background: Thromboembolic disease (TED) after knee arthroplasty occurs infrequently in Iran. The aim of this study was to examine the incidence of TED in patients with osteoarthritis undergoing knee replacement in Southern Iran while on prophylaxis.

Materials & methods: In a case series study from January to December 2012, 100 consecutive total knee arthroplasty (TKA) candidates were evaluated for TED by clinical evaluation and Doppler sonography preoperatively and 2 months postoperatively and by clinical evaluation one year after surgery. The patients in this study randomly received either warfarin or enoxaparin prophylactically.

Results: A total of 77 women and 23 men with mean age of 67 years (52–82 years) entered the study. The average hemoglobin drop of 2.7 g with warfarin and 3.3 with enoxaparin was observed. No case of TED, pulmonary embolus (PE), major bleeding, post-thrombotic syndrome, or hemarthrosis was observed.

Conclusion: No clinically significant DVT was found using either enoxaparin or warfarin prophylaxis after TKA in Southern Iran. Relatively excessive postoperative bleeding was observed, particularly with enoxaparin.

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1. Introduction

Thromboembolic disease (TED) is a potentially serious complication after joint replacement. The reported incidence of this condition varies from 40% to 80% without the use of prophylactic chemotherapy or physical modalities. Pulmonary emboli (PE), which may be fatal in 2% of cases, have been asymptomatic in 10%–20% and symptomatic in 0.5%–3% of patients.^{1–3} Anticoagulants can lower the TED risk down to 15%–30%.^{4,5} Warfarin is probably the most predictive agent

for thromboembolism prophylaxis following total knee arthroplasty (TKA).⁶ The drug is safe, inexpensive, efficient, and can be administered orally. However, the need for its prolonged use of several weeks, its delayed onset of action, its potential to cause drug interactions, and the requirement of frequent INR monitoring are untoward effects.⁷

In contrast, low-molecular-weight heparin (LMWH) can be given for a shorter period of time and does not require regular monitoring of coagulation factors. However, it has the potential for antiplatelet antagonism, is associated with an increased incidence of bleeding, is expensive, and requires

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<http://dx.doi.org/10.1016/j.jor.2014.01.003>

administration by the subcutaneous route. In addition, its use with epidural anesthesia has been associated with major neurologic complications.^{7,8}

The newer oral anticoagulants that exert their action on factor Xa or through the direct inhibition of thrombin do not require coagulation monitoring, but are more expensive than warfarin. There is also no medication available for the rapid reversal of their effects. There have been multiple studies comparing this group of oral agents with enoxaparin with variable outcomes.^{9–11} The bleeding tendency with these agents has been reported to be greater than enoxaparin in some papers, and less in others.^{12,13} A meta-analysis performed by Dahl et al suggested a greater bleeding risk of up to 40% in association with enoxaparin than with these newer agents.¹⁴

The incidence of TED may be different in various populations or ethnic groups. There may also be a relationship between TED and the amount of postoperative bleeding in knee arthroplasty patients. The purpose of this study was to examine the occurrence rate of TED in a case series of patients with knee osteoarthritis while on prophylaxis following knee arthroplasty in our particular population and geographic location. At the same time, we compared the effect of warfarin with LMWH in that cohort.

2. Materials and methods

We conducted a prospective study of patients with knee osteoarthritis undergoing TKA by the senior author with one particular implant and with similar perioperative care from January–December 2012. The study was conducted to evaluate the incidence of thromboembolic disease. All patients in the study were candidates for TKA, were 50 years of age and older with knee osteoarthritis who had none of the exclusion criteria. All patients provided informed consent to randomly receive either warfarin or enoxaparin for TED prophylaxis at their own expense. They also agreed to pay for preoperative and postoperative Doppler sonography. Excluded from the study were patients younger than 50 years of age, patients with inflammatory or crystal arthritis, patients taking regular aspirin or other anti-inflammatory medications or any anti-coagulant for cardiac problems, and patients with a prior history of thromboembolic disease. For the study, TED prophylaxis was restricted to pharmaceutical measures with warfarin or enoxaparin (i.e., no mechanical prophylaxis). Simple randomization was conducted by providing warfarin to the first and every other patient and enoxaparin to the second and every other patient. This was continued until the calculated 100 cases were reached that would be appropriate for the number of TKAs performed in a year at the main referral clinic of the senior author in the Southern part of Iran.

Prophylaxis was provided with “LMWH” by way of a single subcutaneous injection of 40 mg of enoxaparin administered a few hours postoperatively. This was continued with a daily dose of 40 mg for five consecutive days in one group. The other group received 5 mg of warfarin in the immediate postoperative period and single daily doses of warfarin for one month. The target INR was 1.7–2.0 for this group of patients.

Study patients completed general health status, arthritis, and outcome questionnaires (SF36 and WOMAC), as well as a Knee Society Score (KSS) survey.^{15,16,17}

The procedures were all performed by a single surgeon using similar technique, under general anesthesia, and using a uniform type of prosthesis [cemented NexGen Legacy Posterior-Stabilized (NexGen LPS; Zimmer, Warsaw, Indiana)] using intramedullary femoral and extramedullary tibial guides, without any patellar resurfacing. All the cases were performed under tourniquet control. Sources of bleeding were fully cauterized with the tourniquet deflated before wound closure. All patients received uniform postoperative care, including soft cotton bandaging, active knee motion and ambulation within the first 24 h of surgery with the help of a physiotherapist. Continuous passive motion (CPM) was not administered. All patients were discharged with a small tensor bandage around the knee on the fifth postoperative day. The first postoperative clinic follow-up visit was two weeks after surgery. The second visit was two months after surgery, in which a repeat Doppler ultrasound was obtained (all patients received color Doppler ultrasound two weeks prior to surgery and again 2 months after TKA). Sonographic studies were all performed by one radiologist or sonographer with special interest and expertise in vascular sonography. The sonographer was blinded to the type of TED prophylaxis that the patients were receiving.

Any time that TED was suspected in the early days or weeks following surgery, additional Doppler ultrasound was obtained prior to the 2-months follow-up visit.

At the one-year follow-up visit, patients received a clinical evaluation for possible post-thrombotic syndrome (PTS) and were asked questions regarding leg or chest pain, leg swelling, ulceration, or any other symptom or sign suggestive of TED.

Patients paid all expenses for the medications and sonographs required for the study with no contribution from any drug company or third party. No funding was provided by any research or pharmaceutical center or company for the study.

3. Results

The 100 patients with primary knee osteoarthritis included 23 men and 77 women with an average age of 67 years and 11 months (52–80 years). There were 13 patients younger than 60 years of age, 72 between 60 and 74 years of age, and 15 older than 75 years of age.

In terms of risk factors for TED, the average BMI was 29.1 (20.3–39.3). This value was 27.2 for men (39% normal weight, 35% overweight, 26% obese) and 29.7 for women (10.4% normal weight, 44.1% overweight, 45.5% obese). Overall, in accordance with WHO criteria, 42% of patients were overweight and 41% were obese,¹⁸ whereas 40 patients from the warfarin and 43 from the LMWH group were classified as either overweight or obese (Table 1).

Other risk factors for TED in study patients included prominent varicose veins in the lower limbs in four patients, wheelchair ambulatory status in six patients, and breast cancer in four patients. One patient had a history of cerebrovascular accident (CVA), but was on no medication. A previous history of thromboembolic disease was not present in any patient. Patients had other associated diseases that were not

Table 1 – Risk factors for DVT in 100 cases of Knee arthroplasty.

Group	Mean age	Female	Male	BMI			Varicose vein	Wheelchair bound	Breast cancer	CVA
				Normal	Over weight	Obese				
Warfarin	67.2	37	13	10	18	22	2	4	2	–
LMWH	68.6	40	10	7	24	19	2	2	2	1
Total	67.9	77	23	17	42	41	4	6	4	1

necessarily known high-risk group of illnesses, including 14 patients with type II diabetes mellitus, 62 patients with hypertension, and 13 patients with coronary artery disease, three of whom had already undergone bypass grafting.

In terms of calf swelling, 10 patients, four from the warfarin group, and six from the enoxaparin group had swelling with tightness of the calf on palpation and equivocal Homan's sign in the first two or three weeks following knee replacement. These patients underwent additional earlier ultrasounds (sooner than two months) and all turned out negative for deep vein thrombosis (DVT).

No evidence of TED or PTS (e.g., pain, persistent swelling, leg ulceration) was observed at one-year follow-up in any patient.

In 99 patients, postoperative Doppler ultrasound was negative. One patient dropped out of the assigned postoperative ultrasound because she lived too far away; however, she reported having no symptoms. The preoperative ultrasound was normal in 97 cases, and there was evidence of an old partial occlusion of the popliteal vein in two patients, as well as complete thrombosis in another patient.

The average hemoglobin drop was 2.7 ± 0.94 (1–4.6) for warfarin, and 3.3 ± 1.07 (1.2–5.6) for the LMWH (enoxaparin) group. The drop of hemoglobin for warfarin was significantly lower than the LMWH group ($P < .001$). A mean blood transfusion of 1.8 units was required for 10 (20%) patients from the LMWH group, and 7 (14%) patients from the warfarin group.

The average tourniquet time was 50 min (30–100 min). No patient had excessive hemarthrosis requiring aspiration. However, there were ecchymotic skin blotches around the knee or on the leg or thigh in the majority of cases. The areas of ecchymosis were not measured to recognize a clear size correlation with the type of TED prophylaxis. Furthermore, there were clearly wider areas of subcutaneous ecchymosis in those who had received enoxaparin. No major drop in platelet count was observed.

There were no deaths among the group of 100 patients during the first year post-TKA. All the patients were satisfied with their surgery, and the SF36 and KSS surveys demonstrated outstanding improvement. Preoperative scores for the SF36, WOMAC, and KSS surveys were as follows: SF36 (57 ± 3); WOMAC (57 ± 5); and KSS (104 ± 8). Postoperative scores for these surveys at the one-year follow-up were: SF36 (71 ± 5); WOMAC (44 ± 4); KSS (133 ± 32). No statistically significant difference was observed between the two groups ($P < 0.001$) with regard to these scores.

4. Discussion

Thromboembolic disease is a real issue of concern in patients requiring knee arthroplasty.^{1,2} However, there are

controversial reports on this matter in the literature. In a study by Cordell et al,¹ a 57% DVT rate (11% proximal emboli) was observed in TKA patients receiving no chemical prophylaxis, only below-knee compression stockings and early mobilization following surgery. Sach et al¹⁹ compared a group on warfarin with a group that had not received any TED prophylaxis for TKA. They found no extra protection from clinical TED with the use of warfarin, but recognized higher rates of deep wound infection, gastrointestinal bleeding, and other complications with the prophylaxis. The more general idea is in favor of using some form of prophylaxis in knee arthroplasty procedures.^{13,20}

However, the problem remains in implementing an effective prophylactic measure associated with few side-effects (particularly bleeding into the surgical site), ease of administration and monitoring, lower cost, and rapid reversibility.⁹ The safety in terms of minimal bleeding into the surgical site is still a major concern.^{7,11,21} The newer oral medications that inhibit factor IXa or Xa, or thrombin, and do not require repeated coagulation testing give also the promise of more affordable cost, easy administration, and reasonable preventive effect.²² Compared with enoxaparin, dabigatran and rivaroxaban given in the first few hours after surgery have been found to be associated with a lower DVT and PE and a similar risk of bleeding events.²³ In one study, ximelagatran was compared with warfarin and resulted in superior TED prophylaxis, but major bleeding events were encountered more frequently.²⁴

The use of mechanical prophylaxis (alone or in combination with pharmacologic agents) has also been extensively studied. Freeman and colleagues reviewed 50 different studies, and found the lowest reported distal DVT with pneumatic compression. DVT in the proximal veins was, but lower when warfarin or LMWH was also used.²⁵

Warfarin has been an effective form of prophylactic chemotherapy for a very long time.^{26,27} The orthopedic community has learned that a very high prothrombin time is not necessary for protection against DVT. Vives et al, in a randomized prospective study and with only clinical evaluation, recognized a DVT rate of 4.6% using a small dose of 2 mg daily warfarin and 7.1% when warfarin dose was adjusted to obtain an INR of 1.4–1.8.²⁸ They concluded that the efficacy was similar between the two groups. A higher complication rate with the aggressive use of prophylaxis has been observed when using the ACCP (American College of Chest Physician) Grade-1A protocol.²⁹

In the present study, the INR was maintained in a range of 1.5–2 and protection against TED was observed with one-month administration of warfarin. The INR values were checked every three days and a good prophylactic level was achieved with 2.5–5 mg of daily warfarin within the first week.

A similar finding with warfarin has been reported in the literature with some differences in the duration of administration and target anticoagulation levels.^{26,27} However, the patients did all have pre- and postoperative Doppler sonography.

In this study, enoxaparin also provided adequate TED prophylaxis with a once daily injection for five days, with no complications, such as wound problems at the injection site. However, there was a greater tendency for ecchymosis in the leg and thigh and around the knee with enoxaparin, compared with warfarin. There was also a greater hemoglobin drop in the enoxaparin group requiring blood transfusion in 10 patients ($P < 0.001$). Colwell et al, in a multi-center study with short term use of chemoprophylaxis, found more bleeding and a greater need for transfusion with enoxaparin compared with warfarin.³⁰ However, their mean operative blood loss was 500 mL, much less than that in our patients.

The possibility of developing DVT following hospital discharge is a well-recognized fact. It has been suggested by Planes et al that about 20% of patients with hip or knee arthroplasty who have had no DVT at discharge will show DVT on a venography performed one month after surgery.³¹ We did not use venography, but the Doppler sonography performed two months after surgery did not show any evidence of proximal or distal thrombosis, and no case had any evidence of post thromboembolic symptoms in the one-year follow-up.

The use of warfarin and LMWH has been compared in various studies in the past. Warfarin has been often used for knee arthroplasty aiming for a target INR of 2.5 (range, 2–3).³² Enoxaparin, although requiring no INR monitoring, has been associated with increased bleeding and hemarthrosis. The need for surgical evacuation of hemarthrosis was three times greater with enoxaparin, compared with warfarin.^{29,33} It is possible thrombocytopenic side-effect, though rare, can also be a major drawback for its use. We aimed at an INR range of 1.5–2 with warfarin to lower the chance of wound hematoma. Enoxaparin was also given for only five days with smaller dose of only 40 mg per day to make the thrombocytopenic effect less likely.³⁴

We did not see any case of TED or PTS in our patients. The absence of TED in these patients is by itself fairly unique. Whether there is an ethnic difference in the prevalence of TED in the Asian population has been raised and debated in past studies. An incidence of 43% DVT following knee replacement was reported by Leizorovicz et al in an Asian population that did not receive any prophylaxis compared with an incidence of 40%–84% of DVT in Western countries.³⁵ A paper on Japanese patients reported 4% DVT and 0% PE following knee replacement.³⁶ Piovella and colleagues reported on a large group of patients from seven different Asian countries that received no chemotherapeutic TED prophylaxis for their TKA. In 58% of cases there were venographic changes suggestive of DVT, but 60% were asymptomatic.³⁷ In contrast, this paper and others have suggested that DVT in Asian people has fewer tendencies to become symptomatic.³⁵ Asians living in America have been also showing a lower rate of symptomatic thromboembolic disease as compared with American or European people.³⁸ There still appears to be an uncertainty about DVT rates in Asians. Different rates between patients from Korea, China, Singapore, etc. have also been observed.³⁷

Therefore, it is possible to have a different tendency for TED in Iranian population as well. The blood loss in our patients was greater than in other reports of TKA patients.^{30,39} The higher average bleeding, with a mean hemoglobin drop of 2.7 g, is probably another point in favor of decreased DVT incidence. The procedures in our study were all performed under tourniquet control (average tourniquet time of 50 min) with no regional anesthesia, and sites of bleeding were all cauterized before wound closure under standard conditions. The main blood loss seemed to occur primarily in the first 24 h after surgery. This suggests that greater blood loss and lower incidence of DVT are not a result of technical problems, but are likely related to a genetic or ethnic difference.

There were some limitations to the present study. Venography, the gold standard for TED evaluation, was not used in this study. The authors realize that minor, clinically non-significant DVT could have been missed on Doppler ultrasound, but invasive venography was not found justifiable to our Ethics Committee. Silent, small PE was not tested for either in this study. However, there was no case of DVT, PE, or TES, in either patient group. We also recognize that the number of patients in our study was small compared with multicenter studies on DVT prophylaxis. On the other hand, the uniformity of this small case series in terms of performing surgeon, surgical technique, postoperative care, and rehabilitation regimen, are all positive aspects of this study.

The importance of using a prophylactic measure for the prevention of TED in knee joint replacement is well-accepted. The orthopedic community and chest physicians agree that an agent should be used for prophylaxis that is safe, efficacious, and easily reversible.⁴⁰ We used two known agents, warfarin and enoxaparin in 100 consecutive patients with knee osteoarthritis who underwent TKA in Southern Iran. TED was well controlled when either of the above agents was used in a low dose and for a short period of time. There was more blood loss with enoxaparin compared with warfarin, but no major bleeding incident was encountered. In general, a higher postoperative blood loss and lower incidence of DVT compared with reports in the literature could suggest dietary, ethnic, or genetic differences in the population studied.

Conflicts of interest

All authors have none to declare.

Acknowledgments

The authors acknowledge the great assistance of Miss Fariba Boukaee RN in corresponding with the patients and collecting the data for this paper.

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