Original Article

Heparin versus enoxaparine for prevention of asymptomatic deep venous thrombosis after total knee arthroplasty

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Summary:

Background: Venous thromboembolic disease (VTED) is a well known complication that occur following total knee arthroplasty (T.K.A). One of the (VTED) forms is asymptomatic deep venous thrombosis with an incidence has been estimated to be up to ≥ 20% in patients undergone primary T.K.A , despite routine treatment with heparin postoperatively.

Objectives : is to assess the prevalence of post-operative asymptomatic D.V.T among patients receiving two different thromboprophylactic drugs after T.K.A.

Patients and methods: 68 patients who had T.K.A were randomly divided for the purpose of post-operative thromboprophylaxis into two groups , group [A] (control group) consisted of 35 patients received heparin, and group [B] of 33 patients received low molecular weight heparin (L.M.W.H) (enoxaparin) subcutaneously. Both groups were given the drug for two weeks post-operatively, then aspirin untill the 6th week after surgery. Bilateral Duplex U/S performed preoperatively and postoperatively at 5-7 days. The third ultrasonography was performed on the third week after surgery on all patients. the evaluation of the result expressed as primary efficacy outcome which was the composite of D.V.T (either symptomatic or detected by Ultrasonography if the patient was asymptomatic). Non-fatal pulmonary embolism or death from any cause at 42 days after surgery, were also evaluated with a confidence interval (C.I.)

Results: The overall incidence of asymptomatic D.V.T was 2.94% (2 in 68 patients). Those two patient were in heparin group; (group [A]) which represent 11.4% that is highly significant, while no cases (0%) reported among enoxaparin group; Group [B].

Conclusion: Enoxaparin significantly lowered the prevalence of deep vein thrombosis (D.V.T.) after T.K.A.

Key words: D.V.T, enoxaparin, heparin T.K.A.

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Introduction:

One of the most significant complications after T.K.A is the development of D.V.T. a possibility that may result in a life threatening pulmonary embolism (P.E) . although the incidence of symptomatic D.V.T and PE are low, the incidence of asymptomatic D.V.T has been estimated to be ≥ 20% of patients undergone total hip and knee arthroplasty, thus the number of this complication is likely to rise commensurate with the predicted increase in the volume of these procedures (1), the overall prevalence of D.V.T after T.K.A without prophylaxis has been reported to range around 40% - 84%. The risk of asymptomatic P.E may be 10% to 20%, with symptomatic P.E of 0.5% to 3% of the patients, and a mortality rate of 2 %(2).Clinical examination is unreliable in detecting D.V.T, venography is still considered to be of gold standard, but it carries the risk of anaphylactic reaction and small risk of D.V.T, Duplex ultrasonography has arthroplasty (2, 3).It is documented to be sensitive in 67% , 68% , 52% (Eriksson et al (3) Davies et al (4) and Norman et al (5)) respectively.Ultrasonography is useful especially as a screening test with minimal morbidity, low cost, and repeatability of minimal patient discomfort. It needs expert ultrasound technologist.Many pharmaceutical thrombophylaxis agents are available such as warfarin (Vit K anatagonist), heparin (Antihrombin II) low molecular weight heparin (L.M.W.H.) (enoxaparin) (AntiXa), fondaparinux and aspirin. Enoxaparin has bioavailability approximately 80%, and Peak plasma concentration achieve in 2.5 to 4 hours. Recent dose finding studies in patients undergoing T.K.A showed close correlation between the pharmacokinetic and pharmacodynamic effect of enoxaparin (6). The benefit of this medication include a standard dose regimen, absence of routine laboratory monitoring but it should be used with caution in epidural or spinal anesthesia, its usage recommended by the American college of chest physicians for 10-14 days duration a prophylaxis after T.K.A (6) .In this study, (enoxaparin) and heparin as a control group used as a prophylaxis after T.K.A for 14 days in patients without previous D.V.T due to various causes, the Aim is to evaluate the primary efficacy outcome of

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each for further reduction of D.V.T risk postoperatively.

Patients and methods:

This is a prospectve randomized controlled clinical trial conducted on 70 patients undergone primary elective unilateral knee arthroplasty for osteoarthritis at the orthopeadic department of Nursing –Home Hospital of the Medical City complex, during the period from August 2010 to September 2011. There were 35 men and 34 women, their age range from 49-71 years. With weight range (60 kg-113kg) and body height 145 cm – 181 cm . and BMI of 19.84 – 38.45 kg/m^2.All patients before surgery were informed by providing consent form to participate in the study. The exclusion citeria were: (1) patients with a recent thromboembolic disease, i.e. D.V.T or P.E (2) patients scheduled to undergo staged bilateral T.K.A (3) those with active bleeding, (4) patients with severe liver or renal impairment (creatinine clearance < 30 ml per minute), and (5) patients with uncontrolled diabetes mellitus, Rheumatoid arthritis, post-traumatic knee joint arthritis. Bilateral Duplex ultrasonography was performed within one week preoperatively for all patients. Those with asymptomatic D.V.T in the distal or proximal veins had been excluded (two patients).

Study design and drugs: The patients before surgery were randomly assigned to be one of two groups according to admission schedules. One group (A) consisted 35 patients were assigned to receive 5000 I.V of heparin twice daily subcutaneously 6 hours after surgery for 2 weeks postoperatively, and group (B) which consist of 33 patients who received 4000 I.V of Enoxaparin, (Glexane / Sanofi :- Avantis) administered by subcutaneous injection started by 6-8 hours after wound closure , then the drug administered every 24 hours (range 22-24 hours). In the evenings, up to day 14 (range 13 – 17 days) after surgery with the day of surgery defined as day1. aspirin given thereafter till 6th post – operative week for both groups32 patients with Rt. T.K.A and 36 with left T.K.R, all surgeries performed under general anesthesia, three patients given spinal anesthesia, with Ismarch tourniquet control and uniform cemented Zimmer PC Nex-Gen design. Targocid I.V or cephalosporin is given as prophylaxis against infection postoperatively.Patients underwent mandatory bilateral U/S Duplex of both lower limbs at the end of 1st postop. Week, range 7-9 days. And a third U/S at the 2nd week range (15-17 days) and patients had a visit one month after the last dose of the study drug.

Uniform postoperative protocol which include bed side continuous passive motion, muscle strengthening regimen is performed.Statistical analysis done using SPSS (static package for serial sciences for windows V.16.31, the primary efficacy outcome was the composite of any D.V.T., non-fatal PE , or death from any cause up to 30 days (range 30 – 40) after surgery(C.I).The main secondary efficacy outcome was major venous thromboembolism VTE) which was defined as the composite of proximal D.V.T, non-fatal PE, or death from V.T.E.Other outcomes included non-major bleeding, hemorrhagic wound complications (wound hematoma, reported surgical site bleeding or any cardiovascular events classified as on treatment events).Patients were included in the assessment for major venous V.T.E if proximal veins could be evaluated on U/S regardless of whether the distal veins could be evaluated.

Results:

The preoperative U/S clarified the overall prevalence of asymptomatic D.V.T was 3.45%, two out of 70 patients, those two had been excluded from the study, the remaining 68 patients (in both groups) subjected to this analysis. (Table 1)

Table (1) Clinical characteristic of the patients

Characteristic	Heparin No. = 35	enoxaparin No. = 33
Age yr mean range	 63.1 49 - 71	 65.8 52 – 70
Sex female male	 17 (48.6%) 18 (51.4%)	 18 (54.5%) 15 (45.5%)
Body mass index Mean Range	 25.8 15.6 – 58.2	 28.7 16 – 53.1
Sit of operation Lt. Rt.	Lt. 18 Rt. 17	Lt. 20 Rt. 13
Weight – Kg mean Mean range Height : range 145-181 cm	 78.1 kg 48 - 93 kg	 68.8 kg 52 – 89 kg
History of V.T.E	0%	0%
(Prevalence) no% (pre – op.)	35	33
Previous orthop. Surg. No%	nil	Nil
Type of surgery no% Primary Revision	 35 (100%) 0	 33 (100%) 0
Use of cement – no%	35 (100%)	33 (100%)
Type of Anesthesia – no% g.A g.A + Regional Regional only Missing data	 32 ----- 3 ----	 31 ---- 2 ----
Duration of surgery – min Mean Range	 91.3 75 - 120	 94.2 80 – 120

The second U/S, 7–10 days postoperatively to all patients showed no cases of D.V.T.

The third U/S which has been performed 3 weeks after surgery had found 2 patients in the heparin group (A) with D.V.T ;(56 years female and 69 years old male patients , with BMI 29.4 in the operatively treated limb (left side).

The overall incidence of post-operative asymptomatic D.V.T was 2.94 (two of 68 patients), it represent (11.4%) among heparin group. No cases reported among enoxaparin group (table 2).

Table (2) Incidence of efficacy events

	Primary efficacy. Outcome	Major V.T.E	Death during TR	P.E non fatal	D.V.T		VTE symptomatic		Death during follow up
					Prox.	Dist.	During treatment	During follow up	
Heparin/ no. total events	2/35	0/35	%	%	1	1=2	2	%	%
Enoxaparin / no. with event	0%	%	%	%	%		%		%
P. value	<0.001				0.1 1.9		0.4	0.22	%
Absolu. Risk redu. Absolute (-2.6)					-1.9		0.7 (-0.3)		

Table (3)2x2 table of incidence of D.V.T among patient groups

	D.V.T			O.R	P value
Patient -group	positive	negative	total		
enoxaparin	0%	33 (64.3%)			
Heparin-group	2 (1.8%)			1.8	0.0002
Total	2 (1.8%)				

The odds ratios (OR) is 1.8 and the p-value 0.0002 (table 3).The primary efficacy outcome occurred in 2 patients (2.94%) of the heparin group.Non of 33 patients of the enoxaparin group 2.5 percentage points, 95% had DVT a confidence interval (CI) 1.5 to 3.6.In the heparin group weighted risk reduction was 2.6 percentage points.

Discussion

This study showed that enoxaparin has potential superiority in the thromboprophylaxis after T.K.A surgery. And more effective in preventing V.T.E events. P.E or death particularly among patients receiving it , as compared with those received heparin, there was an absolute risk reduction of 2.6% (relative risk reduction , 70%) for the primary efficacy outcome of D.V.T and P.E , or death from any case and absolute risk reduction of 1.7% (relative risk reduction, 88%) for major venous thromboembolism.The superior efficacy of enoxaparin was not associated with any significant increase in the incidence of major bleeding , which was lower than reported in several other studies (Benegt et al(7) , Johanson et al(8)) . This might be due to the difference in the definition of the major bleeding which may necessitate blood transfusion or wound bleeding (Collagon et al (9)). In this study there was one patient who had 2 pints of blood transfusion, Collagon et al regarded wound bleeding is a major index of risk factor, in his 85 patients Study the weighted absolute risk reduction for the primary efficacy outcome in the enoxaparin group as compared with heparin was 2.7% (95% C.I. , 1.6 to 3.8). Furthermore our study showed that extended thromboprophylaxis with enoxaparin for 2 weeks resulted in no incidence of thrombosis with safety profile similar to that of heparin a conclusion had been supported by Greets et al (10) and Pellegrni et al (11), in their 120 patients at different age group after T.K.A., but they included in their study T.K.A. for Rheumatoid arthritis, an issue which may need a separate detailed study.The asymptomatic D.V.T reported in group A postoperatively noted that only in one patient where surgical procedure lasted more than 120 minutes, a time more than usual with other patients, (a female patient), the hospitalization time in both groups was similar, one week (range 5-8 days) a finding correlated with that of Parvizi (12) Barrach (13) Eriksson et al (3). Although they have a hospitalization stay more than one week for most of their 85 patients in their study. The Odd Radio (OR) of 1.8 and P-value of 0.0002 is highly significant, i.e. patients receiving heparin about 2 fold (OR = 1.8) more likely to be liable to develop D.V.T than those using enoxaparin. In the present study there was no statistical significant association between D.V.T development and BMI, age, side of operation or patient's gender, or well controlled co- morbidities e.g diabetes mellitus and hypertension, a finding supported by Erikson et al (13) and Turpie et al (14), Whom diabetic patients constituted 18% and 12% of there 1670, 1018 patients respectively.One patient with asymptomatic D.V.T was in his calf veins while the other was in the popliteal vein, there was no femoral or iliac venous involvement (proximal), as well as no P.E,both patients were normotensive and nondiabetics.Heit et al (15) reported four proximal thrombosis in 1686 patients (0.2%) of the enoxaparin group while it occurred in three of 1678 (2%) of heparin group with absolute risk reduction of 1.7%, 95% C.I., 1 to 2.5: P < 0.001), he included multiracial patients; Hispanic, Black, Asian.

Absence of clinical signs of D.V.T like leg swelling, calf pain or tenderness, or Homan's sign does not preclude D.V.T; therefore meticulous clinical and U/S examination is mandatory to deal with in order to avoid fatal consequences.

Conclusion

This study in spite of its relatively small number demonstrate that thromboprophylaxis by enoxaparin is more effective than heparin in preventing post –operative asymptomatic D.V.T among patients undergone total knee arthroplasty and does not increase the risk of clinically relevant bleeding.

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