Elumalai et al., Orthop Muscul Syst 2015, 4:1
DOI: 10.4172/2161-0533.1000181

Orthopedic & Muscular System: Current Research

Research Article Open Access

Comparison of Efficacy of Low Molecular Weight Heparin Versus Oral Anticoagulant in Indian Population for Prevention of Deep Vein Thrombosis in Total Knee Replacement

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Abstract

Nearly 50% of patients who undergo TKR develop symptomatic/ asymptomatic DVT without prophylaxis. Since LMWH is costly, subcutaneous injection and inconvenience to patient, Oral anticoagulant is used as alternative. It is a prospective study where patients were observed for 15 days, following TKR. The effectiveness of LMWH Vs Oral anticoagulant in Indian population was done comparing 100 patients who underwent TKR. Inclusion criteria - age more than 18 years, under any anesthesia, Indian origin. Exclusion criteria were head injury, abdominal injury,poly trauma, history of DVT, indwelling epidural catheter. Oral anticoagulant used in the study Dabigatran etexilate 220 mg OD or Apixaban 2.5 mg BD for 15 days. Patient was done colour doppler pre-operatively, POD-(3-5) and (13-15). In 100 patients, 25 patients were given Dabigatran, 25 were given Apixaban and 50 were given LWMH. The absolute risk difference - 1.1% in favour of oral anticoagulant. Thus oral anticoagulants was non-inferior to LMWH (P<0.0001). Major bleeding occurred in 2 patients in oral anticoagulant group but none were fatal or required discontinuation of drug. The study showed both oral anticoagulants given for 15 days were as effective as LMWH for prevention of DVT in TKR. Oral anticoagulant proved to be non-inferior to LMWH. Oral anti-coagulant is effective, well tolerated, low rate of bleeding, no evidence of elevated liver enzymes or acute coronary events when compared to LMWH.

Keywords: Prophylaxis; Heparin; Knee Replacement; Anticoagulant

Background

One of the high risk groups for deep vein thrombosis is post orthopaedic surgeries deep vein thrombosis leads to life threatening complication like venous thromboembolism and post-thrombotic syndrome [1-2]. This cause leads to give patient prophylactic anti-coagulants who undergo major orthoapaedic surgery – total knee arthroplasty. Asymytomatic or symptomatic incidence of DVT is nearly 50%. This trial compared the efficacy and safety of oral anti-coagulants versus subcutaneous enoxaparin for prophylaxis in Indian patients undergoing total knee replacements [3-5]. Oral anti-coagulant used in study was dabigatran etexilate and apixaban. Then Patient was followed up for 15 days following the initiation of drug [6].

Materials and Methods

This is a Randomized prospective study (Non-funded) to know the efficacy of low molecular weight heparin versus oral anti – coagulant in Indian population for prevention of deep vein thrombosis in total knee replacement. Inclusion criteria were age greater than 18 years, surgery under any anesthesia, patient undergoing TKR, Indian origin. Exclusion criteria were head injury, abdominal injury, poly trauma, history of deep vein thrombosis, indwelling epidural catheter.

Total number of patients included in the study was 100. 50 patients were started on enoxaparin and 50 patients were stared on oral anti-coagulant (25 patients were given dabigatran etexalate and 25 patients were given apixaban). Enoxaparin was given 12 hours prior to the surgery whereas oral anticoagulant was started post operatively. Dabigatran etexalate was started 6-8 hours after surgery and apixaban was started 12-24 hours after surgery. Enoxaparin was given at a dose of 40mg subcutaneously once daily. Dabigatran etexalate 110 mg stat is given as first dose 6-8 hours after surgery then 220mg orally once daily. Apixaban was given at dose of 2.5mg orally twice daily. In our study detailed history of all the patients was taken and all the patients were evaluated clinically every day for deep vein thrombosis during the stay in hospital. Colour Doppler was done using linear peripheral vascular probe of 12 mega HZ pre – operatively and post – operatively on (3-5) days and (13-15) days. Patients were diagnosed for deep vein thrombosis based on Colour Doppler findings. The primary outcome was to compare the efficacy of oral anti-cogulant with low molecular weight heparin for prevention of Asymptomatic or symptomatic deep – vein thrombosis. The secondary outcome included a composite of major Deep vein thrombosis and its mortality and all-cause mortality during follow-up, and the individual components of primary outcome. The primary safety outcome of both oral anti-coagulant and low molecular weight heparin was studied during treatment period or 48 hours after last dose of administration of drug.

Statistical analysis

The trial was designed to investigate whether 15 days of treatment with oral anti-coagulant was effective as 15 days of treatment with low molecular weight heparin in patient undergoing, total knee replacement and to compare the safety outcomes of the two treatments.

The Primary efficacy analysis was based on patients who underwent total knee replacement and evaluated using colour Doppler. The two sided 95% C I for absolute difference in event rates between oral anti – coagulant and low molecular weight heparin was calculated using normal approximation. Safety outcomes were analyzed using descriptive methods.

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Received November 22, 2014; **Accepted** January 03, 2015; **Published** January 07, 2015

Citation: Elumalai Y, Dorai Kumar R, Anand V, Choudary M, Anandha Prabu V (2015) Comparison of Efficacy of Low Molecular Weight Heparin Versus Oral Anticoagulant in Indian Population for Prevention of Deep Vein Thrombosis in Total Knee Replacement. Orthop Muscul Syst 4: 181. doi:10.4172/2161-0533.1000181

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Results

Patients

Of 100 patients randomized, 50 patients were initiated with low molecular weight heparin. Enoxaparin other 50 patients were initated with oral anticoagulant of which 25 patients were given dabigatran etexilate and 25 patients were given apixaban. Enoxaparin group received their first dose 12 hours before surgery. Dabigatran etexalate group received first dose 6-8 hours post – operatively 110mg state then from next day 220mg orally once daily. Whereas apixaban group took their first dose 8-12hours post – operatively orally twice daily. The treatment duration was 15days. All patients received their study medication in accordance with the study protocol.

Efficacy outcome

The primary outcome deep vein thrombosis and all-cause mortality occurred in 7 of 50 patients in oral anti-coagulant group and 8 of 50 patients in enoxaparin group. Absolute risk difference is -1.1% (95% CI, -3 to -1%) in favour of oral anti – coagulant. Thus, oral anticoagulant was non-inferior to enoxaparin (P <0.0001). In oral anti-coagulants group – 4 of 25 patients in dabigatran drug developed deep vein thrombosis and 3 of 25 patients developed deep vein thrombosis in apixaban group. Again the P value between two oral anti – coagulant drug is <0.0001.

Safety outcome

Major bleeding events during treatment were reported for 2 patients in oral anti-coagulant group and 1 patient in enoxaparin group. None of the major bleeding was fatal or required treatment discontinuation or re-operation. The volume of blood loss during surgery, number of patients receiving blood transfusion and median volume of blood in drain post-operatively was similar in both oral anti-coagulant and low molecular weight heparin.

Characteristic	LMWH (Enoxaparin)	Oral Anti-coagulant (Dabigatran etexalate/Apixaban)
Treated patients	50	50
Age	60(+/-)11	60(+/-)10
female sex	32	34
weight kg	70(+/-)20	70(+/-)20
body mass index	27(+/-)5	27(+/-)5
Creatinine clearance	100(+/-)25	100(+/-)25
RACE – Asian	50(100%)	50(100%)
History of DVT	NIL	NIL
Type Of Anaesthesia		
General	10	7
Reginal	36	38
General & Reginal	4	5
Duration of Hosiptal stay	15(15-28)days	15(15-20)days
Duration of treatment	15 days	15 days
Duration of Study including follow up	15 days	15 days

Table 1: Characteristics of Study.

Outcome	LMWH (Enoxaparin)	Oral Anti-coagulant (Dabigatran etexalate/ Apixaban)	absolute risk difference	P Value
Primary Efficacy outcome	7(50 patients)	8(50 patients)	-1.1	<0.0001
Death	0	0	-	-
Safety outcome major bleeding	2	1	-	0.04

Table 2: efficacy & safety outcome.

Discussion

The results of this study show that oral anti-coagulant (Dabigatran etexilate 220mg once daily, of apixaban 2.5mg twice daily) was non inferior to subcutaneous injection enoxaparin 40mg once daily [7,8]. The primary efficacy outcome observed in this study, 7 patients in oral anti-coagulant group and 8 patients in enoxaparin group. The Absolute risk difference is -1.1% (95% CI- -3 to 1%). P value is <0.0001. The major bleeding occurred in 2 patients belonging to oral anti-coagulant group and 1 patient from enoxaparin group [9-12]. Hence the safety outcome is almost similar to both groups and they do not indicate any clinically relevant difference is safety outcome. Other minor adverse events were nausea, vomiting, constipation, fever, hypotension etc. The Study showed both oral anti-coagulants given for 15 days was as effective as low molecular weight heparin. Oral anti-coagulant are affective, well tolerated, low rate of bleeding, no evidence of elevated liver enzymes or acute coronary events when compared to Low molecular weight heparin. Through various study has been conducted in 2005-07 with more number of cases, it was all conducted only in Europian population [13-15]. This study was exclusively conducted for Indian population which has not been done before [16]. In this study Deep vein thrombosis by is confirmed by using colour venous doppler in all cases since it has high sensitivity and specificity for deep vein thrombosis (Tables 1 and 2).

Conclusion

Oral anti – coagulants proved to be non – inferior to low molecular weight heparin. It is effective, well tolerated, low rate of bleeding, no incidence of elevated liver enzymes or acute coronary events when compared to low molecular weight heparin.

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