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ASPIRIN FOR THE PREVENTION OF DEEP VEIN THROMBOSIS RECURRENCE IN TOTAL HIP REPLACEMENT PATIENTS

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ABSTRACT:

Introduction: Patients who undergo primary Total Hip Replacement (THR) are at high risk for Deep Venous Thrombosis (DVT), the risk of recurrent DVT remains high after anticoagulant treatment is discontinued.

Study objectives: The main objective of this study is to investigate the effect of using aspirin in the prevention of deep Vein Thrombosis Recurrence in Total Hip Replacement Patients.

Methods and subjects: An individual-patient-data analysis of these trials was planned;we analyzed 356 primary total hip replacement cases performed from Mar 2015 to December, 2017. For 6-12months, 200 patients received enteric-coated 100-mg aspirin once daily (the aspirin group) and 156 patients received placebo once daily. There were no considerable differences ($p > 0.05$) in gender, Body Mass Index, or ASA score between the two groups.

Results: We followed our patients for 33 months during which deep venous thrombosis (DVT) recurred in 8 out of 36DVT cases of 156 patients assigned to placebo and in 3 out of 35 of 200 assigned to aspirin (a rate of 21% per year vs. 14.5% per year; 95% confidence interval [CI], 0.51 to 1.03; P=0.04). Aspirin diminished the rate of the expected outcomes of THR; such as the rate of deep vein thrombosis and the recurrence of DVT that was shown to be reduced by 34% by using aspirin (a rate of 9.7% per year with placebo vs. 4.1% per year with aspirin; 95% CI, 0.47 to 0.91; P<0.27). There was no significant difference in the rates of major bleeding episodes (rate of 0.7% per year with placebo vs. 1.2% per year with aspirin, (P=0.21) or serious side effects.

Conclusions: Aspirin decreases the risk of DVT recurrence by more than one third in patients with a first unprovoked DVT in whom other forms of anticoagulants was discontinued, without significantly increasing the risk of hemorrhage in those patients.

KEYWORDS: Aspirin, DVT, Recurrent DVT, THR

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INTRODUCTION:

It is evident that aspirin has a role in DVT prophylaxis post THR, and we still see patients developing recurrence of DVT despite different measures for prevention, there is no much data of the role of aspirin on the long term prevention of DVT recurrence[1]. Unprovoked DVTs still carry a high risk on patients post THR surgeries by converting to pulmonary emboli, so prevention of recurrence should be kept in mind in this patients' category. DVT is a serious disease and its clinical implications might range from edema, pain, venous ulcerations, recurrent DVTs to pulmonary emboli[2].

Risk of DVT recurrence post first unprovoked episodes still occur years after anticoagulation is withhold[3].The risk of recurrence reaches up to 10% during the first year and 5% yearly thereafter[4-6]. Long term anticoagulants such as Vitamin K antagonists are effective but carry a high risk of bleeding and require continuous monitoring and dose amendments, which is troublesome to most of patients[7].

Aspirin has been studied as a preventive measure of DVT recurrence in association with warfarin in the (WARFASA) study, and it is stated as well in the ASPIRE trial that aspirin reduces the recurrence of first unprovoked DVTs by 40% with a safe and tolerable drug profile.

MATERIALS AND METHODS:

A prospective observational cohort studywas carried outduring the period from Mar 2015 to December, 2017 at the Orthopedics department at Prince Hashim Hospital which is a tertiary care center for orthopedics surgeries, a hospital that's affiliated with the Royal Medical Services located in Zarqa, Jordan. We evaluated 356 patients between the ages of 27-71 years with a mean age of 54 years, with no frank risk factors for DVT such as non-ambulatory patients, Cancer, drugs causing hypercoagulability and Pregnancy, etc., patients were evaluated after excluding 15 patients lost on follow up for recurrence of unprovoked, proximal, symptomatic and radiologically confirmed deep vein thrombosis with and without the addition of aspirin 100mg, tablet, patients who had one episode of DVT received other forms of anticoagulants mainly Vitamin K antagonist aiming INR to be between 2.0-3.0, followed by aspirin for 12-24 months. Those who had history of major bleeding event were excluded from this study as well. We consideredmajor bleeding event as a complication of aspirinconfirmed when it was fatal,if a patient had a bleeding in a critical organ such as intracranial, intra-articular, intraocular, pericardial or intrapleural bleeding, or bleeding needing blood transfusion of 2 or more units, or causing a change in hemoglobin of more than 2 g per deciliter as a result of gastric or duodenal ulcer proved by upper endoscopy.

Patients who had THR surgery were given Enoxaparin Sodium 4,500 international units subcutaneously on a daily basis starting 12 hours post operatively and continued for 3 weeks taking in consideration to stop it after making sure the patients are actively ambulating under a qualified physiotherapist supervision, and converting to aspirin 100mg orally, once daily in the first group and one tab of placebo, once daily too in the second group.

We divided our sample in 2 groups; group A (whom received Aspirin) patients was comprised of 200 patients who underwent THR including those whohad unprovoked proximal DVTs post operatively, which were diagnosed by an internist and was confirmed by a radiological diagnosis had been treated by the vitamin K antagonist warfarin for 6-12 months and continued by 100mg aspirin on a daily basis for 1-2 years thereafter. Group B received only placebo, 12 months from having an unprovoked proximal DVT, diagnosed radiologically after vitamin k antagonist was discontinued for 1 year, thereafter.

Patients were followed up on a monthly basis during the first 3 months, every 3 months during the first year then every 6 months and any side effects or related major or minor events were reported. Patients were informed to report any doubtful symptoms suggestive of DVT or bleeding. We lost 11 patients during follow up and 4 patients died during our project implementation.

Of the remaining 341 patients, 227 (66.5%) are females, with a mean age of 53.8years of age, body mass indexis about 32.4±4.2 and 47.4% of the THR patients had their surgery on the right side as demonstrated in (table 1).

SPSS version 18.0 for Windows was used for statistical analysis and P values less than 0.05 were considered statistically significant. Ethics committee at our institution approval was attained at the beginning of conducting this study.

Table 1: Demographics of Aspirin and Placebo groups

	Group A (with Aspirin)	Group B (Placebo)
Number of Patients	192	149
Mean Age (years)	52.6	56.3
Gender (Males)	35.6%	36.1%
Body Mass Index (Kg/m^2)	33.4±4.3	32.3±5.1
Side (Right)	158 (46%)	167 (49%)

RESULTS:

Our sample subjects were selected on a random basis, 200 patients received aspirin 3 weeks post operatively after which they received enoxaparin sodium, except when DVT is diagnosed and confirmed radiologically, vitamin k antagonist was given for 6-12 months followed by aspirin for 12-24 months, thereafter. Of group A patients, DVT recurred in 3 out of 35 patients with unprovoked, proximal DVT (a rate of 14.5% for the first year, P value= 0.04), while in group B, 36 patients had DVT from whom 8 had a recurrence while on placebo, after 12 months of vitamin k antagonist was initiated (a rate of 21% for the first year, P value=0.04). It was also shown that the risk of unprovoked DVTs in the aspirin group was less than in placebo group by 34% with a rate of 19.7% per year with placebo vs. 14.1% per year with aspirin(P<0.27). We also found that there was no significant increments in the rates of major bleeding episodes (rate of 0.7% per year with placebo vs. 1.2% per year with aspirin, P=0.21) or other serious side effects (table 2).

Table 2: Comparison of results between TXA group and control groups

	Group A (n=192) (With Aspirin)	Group B (n=149) (without Aspirin)
Number of DVTs	35	36
Recurrent DVT Episodes	3	8
Major bleeding episodes (N, %)	6 (1.2%)	3 (0.7 %)

We lost 15 patients by the end of our study, 11 patients were lost for follow up, some of them we lost connection with and others refused to proceed in our project, and 4 patients had died, 2 of them were admitted as they were diagnosed to have pulmonary emboli.

In the aspirin group, there were three cases of major bleeding that didn't end up in death, due to peptic ulcer disease treated endoscopically and five patients had nonmajor bleeding, one due to chronic subdural hematoma post minor trauma, and four due to peptic ulcer treated conservatively. In the placebo group, two patients had major bleeding due to peptic ulcer disease and one had subcutaneous hematoma with leg swelling post trauma.

Four patients died while we were conducting our study, two in each group (0.05% per year in the aspirin group and 0.06% per year in the placebo group). Two of them were admitted to the hospital as a case of pulmonary embolism, one in each group.

DVT occurred unilaterally in 38 patients (53.5%) which has no direct effect on the recurrence of DVT on consequent measures. We noticed slightly increased risk in patients above 64 years of age (P value <0.05) and in males rather than in females (P value<0.06).

DISCUSSION:

There are stronger evidences nowadays concerning the role of aspirin in recurrence prevention of unprovoked venous thromboembolism as in the WARFASA study that stated a significant reduction of recurrence with aspirin with no significant increase of major bleeding episodes, this was also proved in the INSPIRE collaboration which showed a one third reduction of recurrence of venous thromboembolism by using aspirin without significantly increasing the risk of major bleeding.Aspirin has the advantage of obviating the need of continuous laboratory monitoring and dose adjustments, its efficacy and cost effectiveness[8]. It is well established that halting anticoagulants predispose patients with unprovoked DVTs for recurrence[9-11], while continuing treatment for DVTs reduces recurrence (12). Our aim of this study is to show that aspirin might replace the use of hazardous long use ofother anticoagulants.

Aspirin has a role in reducing the risk of primary DVTs in patients prone to develop venous thromboembolism[13-17]; this was measured and supported in our study but with an insignificant reduction. Aspirin has a direct effect on platelets which have a direct effect on thrombi formation[16, 17] and reducing the rate of DVTs.

It was shown that aspirin, besides its primary and secondary role in preventing venous thromboembolism has no significant increased risk of major bleeding over placebo, with reported few cases of peptic ulcer disease that were treated successfully, however, placebo group had an insignificantly reduced rate of major bleeding over the aspirin group.

We noticed a greater incidence of DVT recurrence post THR in patients older than 64 years old and higher risk among males in comparison to females. The gender factor didn't show a significant increase, though.

Some of the limitations this study has is the wide exclusion criteria, such as cancer patients, which precluded a significant number of patients with first time DVTs post THR from our study and obscured results that might present to us if those patients were not excluded. We didn't assess the effect of aspirin on the rate of ischemic heart disease and cerebrovascular diseases as those diseases might be associated with DVT in many patients. But on the other hand, this study spent 33 months which is a long time when compared to similar studies.

CONCLUSION:

We deduce that aspirin has a significant reduction rate of recurrence of unprovoked, proximal DVTs post THRwhen used after long use of oral anticoagulants with no significantly increased risk of major bleeding.

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