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Full length Research Paper

Dabigatran as a New Method for Thromboprophylaxis after Gynecological Procedures

Mahmoud Salah Mahmoud
Obstetrics and Gynecology Department, Al-Azhar Faculty of Medicine, Egypt

Abstract
Deep vein thrombosis (DVT) defined as formation of a thrombus in the deep veins of the leg, although DVT may also occur in the veins of the upper limbs. Dabigatran was the first oral direct thrombin inhibitor (DTI) marketed in the United States as well as the first of the group of drugs known as novel or non-vitamin K antagonist oral anticoagulants (NOACs). This is a cross section clinical observation study conducted in Al-Azhar University hospital (New Damietta). This study includes 100 women with high risk factor for thromboembolism undergoing major gynecological operation and started at the period from May 2013 to February 2014*. 50 patients after gynecological operation with risk factor of DVT treated with oral dabigatran and 50 patients after gynecological operation with risk factor of DVT treated with enoxaparin. Enoxaparine is better than dabigatran in Thromboprophylaxis after gynecological procedure. Dabigatran is an effective oral alternative to existing Thromboprophylaxis agents in patients undergoing major gynecological operation. In patients, undergoing major operation should take dabigatran orally to avoid complication as venous thromboembolism and dabigatran considered better than subcutaneous enoxaparin due to easily drug administration.*

Keywords: *DVT, Dabigatran, Enoxaparin.*

Introduction

Common signs and symptoms of DVT include pain or tenderness, swelling, warmth, redness or discoloration and distention of surface veins, although about half of those with the condition have no symptoms. Signs and symptoms alone are not sufficiently sensitive or specific to make a diagnosis, but when considered in conjunction with known risk factors can help determine the likelihood of DVT (Scarvelis and Wells, 2006). Symptoms are more often due to other causes such as cellulitis, Baker's cyst, musculoskeletal injury or lymphedema (Hargett and Tapson, 2008). Dabigatran (Pradaxa®) is an oral direct thrombin inhibitor that can be used with fixed doses, without the need for routine anticoagulation laboratory monitoring and the advantage of few drug or diet interactions. Dabigatran is effective for stroke and systemic thromboembolism in AF and for the prophylaxis and treatment of VTE. The drug has a good safety profile and consistently shows a reduction in intracranial hemorrhage risk compared to warfarin (Ageno et al., 2014).

Dabigatran is a reversible, competitive inhibitor of thrombin, to which it binds in both freely circulating and clot bound forms. Like other NOACs, its mechanism of action does not interfere with the interaction of platelets and platelet factor 4 (PF4) or that of antibodies with the heparin/PF4 complex (Burness and McKeage, 2012). In the active-control study, dabigatran was not inferior to warfarin for the prevention of VTE, once again with a lower risk of bleeding. In the placebo-control study, dabigatran significantly reduced the rate of recurrent VTE but also showed a significantly higher risk of bleeding. The benefit of treatment with dabigatran was maintained during extended follow-up after the study drug was discontinued. The authors noted that the efficacy of dabigatran and its risk of clinically relevant bleeding versus placebo is similar to that of rivaroxaban compared to placebo (Schulman et al., 2014).

Low-molecular-weight heparins (LMWHs) as enoxaparin and vitamin K antagonists are used routinely for Thromboprophylaxis after major orthopedic surgery (Geerts et al., 2004). Although they effectively reduce the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE), a number of limitations restrict their use. Vitamin K antagonists, although orally administered have a slow onset of action, interpatient variability, need for frequent monitoring and potential drug interactions, whereas LMWHs a are administered parenterally (Eriksson et al., 2006).

Materials and methods

Patients and methods

This is a cross section clinical observation study conducted in Al-Azhar University hospital (New Damietta). This study includes 100 women with high risk factor for thromboembolism undergoing major gynecological operation, started at the period from May 2013 to February 2014, and participated after oral and informed consent with the following criteria:

Inclusion Criteria: Patient undergoing major gynecological operation e.g.: Hysterectomy (vaginal, abdominal), myomectomy, ovarian cystectomy, vaginal repair). Risk factor for DVT or Pulmonary Embolism e.g.: previous VTE , known high- risk thrombophilia and medical morbidities e.g. cancer , heart failure, active systemic lupus erythematosus , inflammatory polyarthropathy or inflammatory bowel disease , nephrotic syndrome , type I diabetes mellitus with nephropathy , sickle cell

disease , current intravenous drug user , family history of un provoked or estrogen-related VTE in first-degree relative , known low risk thrombophilia , Age > 35 years , obesity , parity >3, smoker, gross varicose veins.

Exclusion Criteria: Hypersensitivity to dabigatran or enoxaparin., Elevated liver enzymes [ALT] greater than three times the upper limit of the normal range, Severe renal insufficiency [creatinine clearance <30 ml/minute], Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone and Prosthetic heart valves requiring anticoagulant treatment.

The following were taken:

1. Careful history taking to check for inclusion and exclusion criteria according to standardized research protocol.
2. Obstetric history including Gravidity, parity, Multiple pregnancies, Pregnancy induced hypertension and Gestational or pregestational diabetes
3. Past history including medical diseases (DM, Hypertension, Coagulopathies, cardiac and pulmonary diseases….), previous operations or others.

Statistical analysis: Comparison of maternal plasma concentrations of homocysteine with different Doppler scores was carried out using the Kruskal–Wallis test. The significance between the groups was evaluated by the Mann–Whitney U-test with Bonferroni correction. Spearman correlation analysis was performed for correlations of non-parametric variables.

Results

Table 1: Demographic data of studied groups

Variable	Dabigatran (n= 50)	Enoxaparin (n= 50)	P
Age (years) Mean± SD	42.6±6.6	43.4±7.9	0.4
BMI (Kg/m^2) Mean± SD	33.64±1.9	33.69±3.1	0.48
Parity Mean± SD	2.7±1.5	2±1.6	0.16

This table shows that age, BMI and parity were nearly comparable between group treated with Dabigatran and group treated with Enoxaparin (age: 42.6±6.6 Vs 43.4±7.9 years, BMI: 33.64±1.9 Vs 33.69± 3.1 Kg/m^2 and parity: 2.7±1.5 Vs 2±1.6).

Table 2: Surgical characteristics of studied groups

Variable	Dabigatran (n= 50)	Enoxaparin (n= 50)	P value
General anesthesia N (%)	46 (92%)	47 (94%)	0.39
Spinal anesthesia N (%)	4 (8%)	3 (6%)	0.39
Duration of surgery (min) Mean± SD	96±16.9	89.5±21.4	0.2

This table shows that surgical characteristics between group treated with dabigatran and group treated with Enoxaparin. They include general anesthesia (92% Vs 94%), spinal anesthesia (8% Vs 6%) and duration of surgery (96±16.9 Vs 89.5±21.4 min).

Table 3: Efficacy outcomes of studied groups

Variable	Dabigatran (n= 50)	Enoxaparin (n= 50)
Major VTE and VTE related to mortality	4 (8%)	5 (10%)
Total DVT **Proximal** **Distal**	10 (20%) 4 (8%) 6 (12%)	7 (14%) 5 (10%) 2 (4%)
Symptomatic DVT	0 (0%)	0 (0%)

This table shows that efficacy outcomes between group treated with Dabigatran and group treated with Enoxaparin. They include major VTE and VTE related to mortality (8% Vs 10%) and total DVT (20% Vs 14%) which divided into proximal (8% Vs 10%) and distal (12% Vs 4%).

Table 4: Safety outcomes (bleeding) of studied groups

Variable	Dabigatran (n= 50)	Enoxaparin (n= 50)
Major bleeding events	1 (2%)	0 (0%)
Hemoglobin loss	1 (2%)	0 (0%)
Blood transfusion	1 (2%)	0 (0%)
Non-major bleeding events	2 (4%)	1 (2%)

This table shows that safety outcomes between group treated with Dabigatran and group treated with Enoxaparin. They include major bleeding events (2% Vs 0%), hemoglobin loss (2% Vs 0%), blood transfusion (2% Vs 0%) and non-major bleeding events (4% Vs 2%).

Table 5: Other safety outcomes of studied groups

Variable	Dabigatran (n= 50)	Enoxaparin (n= 50)
No (%) of adverse events	29 (58%)	31 (62%)
Drug related to adverse events	2 (4%)	4 (8%)
Patient with wound hemorrhage	0 (0%)	1 (2%)

This table shows that other safety outcomes between group treated with Dabigatran and group treated with Enoxaparin. They include percentage of adverse events (58% Vs 62%), drug related to adverse events (4% Vs 8%) and patients with wound hemorrhage (0% Vs 2%).

Discussion

Guidelines of the RCOG and the National Institute for Health and Clinical Excellence encourage the use of LMWH as Thromboprophylaxis in high-risk pregnancies and during the postpartum period. However, these recommendations were largely based on expert opinion with little evidence from randomized controlled trials and meta-analyses (Wu et al., 2013). With LMWH, extended Thromboprophylaxis is significantly more effective in preventing VTE (Arcelus et al., 2006). Extended Thromboprophylaxis with enoxaparin for four weeks has shown to significantly reduce the incidence of VTE significantly (0.5% vs. 3.27%) compared with short-term Thromboprophylaxis (7 to11 days) in Indian patients (Nair et al., 2013).

However, subcutaneous administration of LMWHs such as enoxaparin for up to 35 days could cause discomfort and makes it difficult for patients to adhere to treatment post-discharge. Switch-therapy modalities have been shown to provide clinicians an advantage of using enoxaparin safely during the hospitalization period and then switch to dabigatran for ease of administration during the outpatient period (Ozler et al., 203). Dabigatran etexilate was as effective as enoxaparin for the primary prevention of VTE, with a similar safety profile (Eriksson et al., 2006).

The present work aimed to compare the efficacy and safety of oral dabigatran, a direct thrombin inhibitor, versus subcutaneous enoxaparin for extended Thromboprophylaxis in patients undergoing major gynecological operations e.g..: Hysterectomy (vaginal or abdominal or caesarian), myomectomy, ovarian cystectomy, vaginal repair and caesarian section in high risk group .In the present study, age, BMI and parity were nearly comparable between group treated with Dabigatran and group treated with Enoxaparin (age: 42.6±6.6 Vs 43.4±7.9 years, BMI: 33.64±1.9 Vs 33.69± 3.1 Kg/m^2 and parity: 2.7±1.5 Vs 2±1.6 with no statistically significant differences) and these agree with Malhotra et al. (2013) who noticed that the mean age 47.7 years at Dabigatran and 50.9 years at Enoxaparin treated group with insignificant statistical differences and also BMI has no statistical significant differences. In the present study, the surgical characteristics between group treated with Dabigatran and group treated with Enoxaparin include general anesthesia (92% Vs 94%), spinal anesthesia (8% Vs 6%) and duration of surgery (96±16.9 Vs 89.5±21.4 min). Eriksson et al. (2011) have published the results of the efficacy and safety of oral dabigatran versus subcutaneous enoxaparin for Thromboprophylaxis after total hip arthroplasty. The surgical procedures mostly involved the use of regional anesthesia in both the Indian and global patients. The first dose of enoxaparin was administered pre-surgery (median 12.6 hours) and dabigatran was administered post-surgery (median 2.8 hours) in all the Indian patients, whereas in the global counterpart, enoxaparin and dabigatran were administered preoperatively as well as postoperatively depending on the local practice followed in that particular country and/or as per the investigator's judgment.

In the present study, the efficacy outcomes between group treated with Dabigatran and group treated with Enoxaparin include major VTE and VTE related to mortality (8% Vs 10%) and total DVT (20% Vs 14%) which divided into proximal (8% Vs 10%) and distal (12% Vs 4%). Rosencher et al. (2009) noticed that the composite of major VTE (proximal DVT and/or PE) and VTE-related mortality occurred in 3.3% (69 of 2096) of the enoxaparin group, 3.0% (62 of 2033) of the dabigatran etexilate 220 mg group and 3.8% (78 of 2071) of the 150-mg group. Major bleeding occurred in 1.4% of the enoxaparin group, 1.4% of the dabigatran etexilate 220 mg group and 1.1% of the 150-mg group. Most of the major bleeding events (80-90%) occurred at the surgical site. Malhotra et al. (2013) reported that major VTE and VTE-related mortality were low in both the arms (7.9% dabigatran and 9.9% enoxaparin) in Indian patients. Fewer patients were diagnosed with proximal DVT in the dabigatran group (7.9% India and 2.1% global population) compared with the enoxaparin group (9.9% India and 3.9% global population). However, in the Indian patients, distal DVTs were more often reported in the dabigatran group (10.7%) compared with the

enoxaparin group (2.7%); whereas in the global population 5.4% and 4.5% of the patients had distal DVTs in the dabigatran and enoxaparin groups respectively. Distal DVTs (associated with calf veins) are less serious than the proximal DVTs as thrombi in calf veins are generally small and have little chance of embolization. Distal DVTs are therefore not usually associated with clinical disability or other complications. Distal DVTs may be at risk of embolization if they extend proximally (Kearon, 2003). The incidence of proximal DVT observed with enoxaparin (2.8%) was lower than that observed in previous studies that used 40 mg enoxaparin (5.2%) (Eriksson et al., 2005) which was similar to that observed in the rivaroxaban (active factor X) twice-daily dosing study (4.7%). The incidence of symptomatic VTE events was low during treatment and follow-up after short-term rivaroxaban (6 to 10 days) (Eriksson et al., 2005). In a prospective study conducted in New Delhi, the overall incidence of VTE was reported to be 6.12% among patients undergoing major surgeries (Bagaria et al., 2006).

The incidence of proximal DVT observed with enoxaparin (2.8%) was lower than that observed in previous studies that used 40 mg enoxaparin (5.2%) (Eriksson et al., 2005). In the present study, the safety outcomes between group treated with Dabigatran and group treated with Enoxaparin include major bleeding events (2% Vs 0%), hemoglobin loss (2% Vs 0%), blood transfusion (2% Vs 0%), non-major bleeding events (4% Vs 2%), percentage of adverse events (58% Vs 62%), drug related to adverse events (4% Vs 8%) and patients with wound hemorrhage (0% Vs 2%). Lassen et al. (2002) reported that there was a significant dose trend for major postoperative bleeding across the rivaroxaban treatment groups. The observed incidences were similar in the 5-and 10-mg rivaroxaban groups and the enoxaparin group (2.3% and 0.7% versus 1.9%, respectively). The observed incidences in the 20-, 30-, and 40-mg rivaroxaban dose groups were higher than with enoxaparin, but no dose group was discontinued because of excessive bleeding. Importantly, there were no fatal bleeding events or bleeding into a critical organ; all major bleeding events were confined to the surgical site. Huisman et al. (2010) reported that there was a 7-fold proportional difference in the rate of major bleeding for patients receiving enoxaparin in trials versus dabigatran than versus rivaroxaban (mean, 1.4% versus 0.2%). This is almost certainly related to recognized differences in the definition of major bleeding.

Only one patient had a major bleeding event prior to the administration of dabigatran as evidenced by a fall in hemoglobin level (>20 g/L) leading to blood transfusion (Malhotra et al., 2013). The observed incidence of clinically relevant, non–major bleeding was lower in all active factor X (rivaroxaban) dose groups than that observed with enoxaparin, and minor bleeding followed the same pattern as major bleeding, with a similar incidence compared with enoxaparin in the lower rivaroxaban dose groups. The proportion of patients requiring transfusion was similar in all rivaroxaban dose groups and the enoxaparin group, and similar to that reported in other clinical trials investigating anticoagulants in patients undergoing hip replacement surgery (Eriksson et al., 2003). Anticoagulants prevent VTE, but the risk of bleeding associated with their use can be fatal. The risk of gastrointestinal bleeding related to dabigatran is similar to warfarin (Abraham et al., 2013). Also, dabigatran and enoxaparin pose a similar risk of clinically significant bleeding, major bleeding and clinically relevant nonmajor bleeding (Gomez-Outes et al., 2012). The occurrence of all adverse events (AEs) in the Indian population was slightly lower (58.2% dabigatran group and 61.4% enoxaparin group) than the global population (67% dabigatran group and 69% enoxaparin group). Occurrence of safety adverse events was more frequent in the enoxaparin (9.1%) group compared with the dabigatran (4.4%) group in the Indian patients. As per the investigator's evaluation, a higher number of drug related AEs were reported in the enoxaparin group (6.8%) than the dabigatran group (3.3%) in the Indian patients (Malhotra et al., 2013). Till now according to our knowledge there is now study published to compare the efficacy and safety of oral dabigatran versus subcutaneous enoxaparin for extended Thromboprophylaxis in patients undergoing major gynecological operations.

Conclusion

Enoxaparine is better than dabigatran in Thromboprophylaxis after gynecological procedure. Dabigatran is an effective oral alternative to existing Thromboprophylaxis agents in patients undergoing major gynecological operation. In patients, undergoing major operation should take dabigatran orally to avoid complication as venous thromboembolism and dabigatran considered better than subcutaneous enoxaparin due to easily drug administration.

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