A Prospective Study Comparing the Effect of Rivaroxaban vs. Enoxaparin Given as a Prophylaxis for Deep Venous Thrombosis in Patients Undergoing Bariatric Surgery

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ABSTRACT

Background: *Obesity is a risk factor for deep vein thrombosis (DVT) and venous thromboembolism (VTE). VTE is the most common cause of mortality in patients undergoing bariatric surgery. There is a remarkable variation in practice regarding methods, dosages and duration of prophylaxis in this patient population. Most of the literature is based on European & American patients and specific guidelines for Egyptians do not exist.* ***Aim of the Work:*** *to compare between obese patients undergoing bariatric surgery who receive Enoxaparin prophylactic dose perioperative and others who receive Rivaroxaban prophylactic dose perioperative, concerning the incidence of development of VTE postoperatively.* ***Patients and Methods:*** *This study was conducted on 40 patients From December 2017 till February 2019. Patients included in the study were essentially attending the Vascular Out-patient Clinic at Ain Shams University Hospitals and Nasser Institute for research & Treatment at Cairo and received postoperative prophylactic doses of Enoxaparin and Rivaroxaban after undergoing bariatric surgeries.* ***Results:*** *This study showed less incidence of DVT in Patients who received Rivaroxaban (5%) than those who received Enoxaparin (10%) but the difference in between the 2 of the was statistically insignificant. In terms of bleeding tendency, both drugs showed no incidence of bleeding tendency.* ***Conclusion:*** *From the previous results, further Randomized Controlled studies should be done on a larger cohort of patients undergoing bariatric surgery to determine the efficacy and to set new guidelines for DVT prophylaxis in bariatric patients bearing in mind terms of efficacy, safety and compliance on therapeutic regimens.*
Keywords: *Rivaroxaban – Enoxaparin - Deep Venous Thrombosis - Pulmonary Embolism*

INTRODUCTION

Surgical approaches to weight loss, bariatric surgeries, are commonly performed procedures for morbidly obese individuals; the estimated number of bariatric procedures in the USA alone was close to 180,000 in 2013. Bariatric surgery is effective in achieving weight loss and improving obesity-related complications [(1)].

Thus, in patients with morbid obesity, i.e., a body mass index of ≥ 40 or ≥ 35 kg/m2 with co-morbidities, bariatric surgery is presently considered to be the only effective therapy for obesity. Extensive data demonstrate that surgery can improve or even reverse many comorbidities such as type 2 diabetes, hypertension, obstructive sleep apnoea and steatohepatitis [(2)].

There are also potential risks or complications, among them venous thromboembolism (VTE). Reported rates of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), following bariatric surgery are 0.3%–2.2%, with rates of PE being approximately 1%, despite application of methods to prevent these complications [(3)].

VTE is a challenging problem after bariatric surgery but there are few randomized controlled trials studying thrombo-prophylaxis in this population. Most bariatric surgery patients carry multiple risk factors for VTE and therefore are at least at moderate risk for VTE postoperatively. Despite the elevated VTE risk, the incidence of postoperative VTE is low. A meta-analysis of 19 studies with 3991 patients demonstrated a weighted mean incidence of PE of 0.5% with fixed-dose chemoprophylaxis and an incidence of symptomatic VTE of 0.6% with weight-based chemoprophylaxis [(4)]. PE is a frequent cause of postoperative mortality in the bariatric surgery population and is a common finding at autopsy [(5)]. The risk of VTE is lower for laparoscopic

compared with open bariatric surgery patients (0.34% versus 1.54%) [6].

Various strategies have been used to prevent VTE in patients undergoing bariatric surgery, including pharmacologic and mechanical approaches. However, the optimal approach remains unclear. Based on the ACCP guidelines, LMWH, unfractionated heparin, or mechanical prophylaxes with Intermittent Pneumatic Compression (IPC) are recommended. There is no consensus on the standard of care for chemo-prophylactic agent, dosing, timing, or duration. Dosing of pharmacologic prophylaxis is challenging in postsurgical bariatric surgery patients because dosing by body weight may lead to excessive anticoagulation and bleeding. Some studies utilize anti-factor Xa levels to determine adequacy of anticoagulation, but therapeutic levels do not necessarily predict a reduction in VTE. The ACCP guidelines recommend consulting with a pharmacist to determine dosing in obese patients [7]. Prophylactic removable inferior vena cava (IVC) filter use had previously been recommended in high risk bariatric patients such as those with BMI >60, severe pulmonary hypertension, or previous VTE. More recent data argues against the use of prophylactic IVC filter placement. In 322 of 97,218 patients who received IVC filters and had either gastric bypass or gastric band, there was an increased risk of DVT, length of hospital stay and mortality compared to the non-IVC group [8]. In this study, there was no benefit for prophylactic insertion of IVC filters. A meta-analysis of prophylactic IVC filters in bariatric surgery demonstrated an increase in the risk of DVT by 3-fold while the increase in mortality was not statistically significant. Long-term complications associated with IVC filters are concerning and most filters are never retrieved. There is insufficient data from randomized studies to support the use of prophylactic IVC filters [9].

AIM OF THE WORK

The main aim of this study is to compare between obese patients undergoing bariatric surgery who receive Enoxaparin prophylactic dose perioperative and others who receive Rivaroxaban prophylactic dose perioperative, concerning the incidence of development of VTE postoperatively.

PATIENTS AND METHODS

Forty three patients who were undergoing surgical intervention for morbid obesity (BMI ≥35kg/m2) were collected, only 40 were enrolled in the prospective study and a single patient was excluded due to presence of DVT two other patients failed to comply to the follow up schedule. The patients included in the study were essentially attending the Out-patient clinics at Ain Shams University Hospitals and Nasser Institute for Research and Treatment in Cairo. They were divided into two groups each group is formed of twenty patients. One group received pharmacological prophylactic doses of Enoxaparin postoperatively, while the other group received pharmacological prophylactic dose of Rivaroxaban postoperatively. The 2 groups were followed up clinically and via Venous Duplex on the lower limbs regularly after one month and after three months of surgical intervention as a screening for clinical or subclinical Deep vein thrombosis. The findings were compared according to the efficacy of both drugs in prevention of postoperative DVT.

Every patient was subjected to:

History taking:

Personal history (name, age, sex & special habits), Complaint (onset, course & duration), History of present illness (Morbid obesity and detailed history of associated comorbidities and chronic illnesses), Risk factors (Prolonged Immobilization, Acute anemia, smoking, Hormone replacements, hormonal contraception), past history (Old DVT, previous major surgery, chronic illness, long term medical treatment, Varicose veins, Chronic venous insufficiency)

General examination:

Pulse, blood pressure, cardiovascular assessment and respiratory assessment.

Local examination:

Inspection: scar of previous intervention, abnormal pigmentation, swollen red calf and thigh, visible varicosities.

Palpation: of femoral, popliteal and distal pulsations.

Laboratory investigation:

Complete blood picture, Blood sugar level, Kidney function tests, Prothrombin time and concentration, D dimer test.

Duplex Scanning:

Duplex scanning is an easy, non- invasive and highly sensitive method for examination of the venous system of both lower limbs. Normally, the veins are compressible and show normal flow direction and velocity with no echogenic mural thrombi. In case of venous thrombosis the veins appear non compressible in case of complete thrombosis and may show mural hypo or hyper echogenic thrombus.

Methods of prophylaxis:

Mechanical:

Bilateral class 2 graduated elastic stockings and gaining mobility as soon as possible.

Pharmacological:

- Enoxaparin group: 1/2 mg/kg subcutaneously once daily for 14 days.
- Rivaroxaban group: 10 mg PO once daily for 14 days.
- They were both initiated 12 hours after surgery.

Selection criteria for our study group:

Inclusion criteria:

- Age: from 18 to 50 years old.
- Sex: males and females.
- Between 35 kg/m2 and 40 kg/m2 and other significant diseases (for example type 2 diabetes or high blood pressure) that could be improved if they lost weight. All appropriate non-surgical measures have been tried but the person has not achieved or maintained adequate, clinically beneficial weight loss.
- The person commits to the need for long term follow up.

Exclusion Criteria:

- Patient with previous history of previous VTE.
- Patients with history of cardiac or chest disease.
- Patient on hormonal replacement therapy or oral contraceptive pills.

Follow up

Follow up was done in the outpatient clinics of Ain Shams University Hospital and Nasser Institute for Research and Treatment clinically and by venous duplex on both lower limbs postoperatively after 1month and 3 months consecutively.

Statistical methods:

Data was recorded in a database sheet which was verified before data entry. SPSS program version 17 was used for data analysis which included: Descriptive analysis, Chi-square test X2 and P-value to find significant relation between two or more percentages for qualitative data:

- Statistical significance if P-value <0.05.
- Statistical high significance if P-value <0.01.
- Statistical not significant if P-value >0.05.

Ethical considerations:

All data was confidential. A written consent was obtained from the patients. Informed consent from these patients to participate in a study about the A Prospective study comparing the effect of Rivaroxaban vs. Enoxaparin given as a prophylaxis for Deep Venous Thrombosis in patients undergoing bariatric surgery.

RESULTS

According to age, patients in Enoxaparin group ranged from 18 to 62 years old, while in the Rivaroxaban group ranged from 18 to 65 years old. While equal distribution of both sexes was found in the Enoxaparin group with 10 males and 10 females, in Rivaroxaban 11 patients were females and 9 patients were males. BMI ranged from 37.6 to 90 kg/m2 with mean BMI = 50.73±14.81 in Enoxaparin group, while in Rivaroxaban group ranged from 40.48 to 62.27 with mean BMI = 47.82±6.42 and the. No statistical insignificance was found comparing the 2 groups. Shown in table 1:

Table (1): Demographic data comparison

		Enoxaparin group	**Rivaroxaban group**	**Test value**	**P-value**	**Sig.**
		No. = 20	**No. = 20**			
Age	**Mean ± SD** **Range**	43.50 ± 11.34 18 – 62	47.35 ± 13.92 18 – 65	-0.959•	0.344	NS
Sex	**Female** **Male**	10 (50.0%) 10 (50.0%)	11 (55.0%) 9 (45.0%)	0.100*	0.752	NS
BMI	**Mean ± SD** **Range**	50.73 ± 14.81 37.6 – 90	47.82 ± 6.42 40.48 – 62.27	0.802•	0.428	NS

On comparing the usage of different modalities for mechanical prophylaxis against DVT in each of the 2 groups of patients, No patient in the 2 groups received IVC filer. 17 patients in the Enoxaparin group used elastic stockings & all patients of the Rivarospire group, the difference between the 2 groups was statistically insignifican. All patients gained mobilizataion after 1-21 days in the Enoxaparin group, while the timing of gaining complete mobilization was in a range of only 1-7 days in Rivaroxaban group in which also the difference was insignificant (Table 2):

Table (2): Prophylactic measures "comparison"

Prophylactic measure		**Enoxaparin group**	**Rivaroxaban group**	**Test value**	**P-value**	**Sig.**
		No. = 20	**No. = 20**			
IVC filter	None	20 (100.0%)	20 (100.0%)	–	–	–
Elastic stockings	No	3 (15.0%)	0 (0.0%)	3.243	0.072	NS
	Yes	17 (85.0%)	20 (100.0%)			
Mobilization after (days)	Median (IQR)	2.0 (2 – 7)	2.0 (2 – 3)	-0.407	0.684	NS
	Range	1 – 21	1 – 7			

Concerning Caprini score values, the Enoxaparin group ranged from 5 to 11 with mean± SD = 6.47±1.61. While in the Rivaroxaban group the range was 5 to 9 with mean± SD = 5.95±1.10 with "P value = 0.241" which was also insignificant. As shown in the table fig. 11, table 3:

Table (3): Caprini Score

Caprini Score	**Enoxaparin group No.=20**	**Rivaroxaban group No.= 20**	**Test value**	**P value**	**Significance**
Mean±SD (Range)	6.47 ± 1.61 (5 – 11)	5.95 ± 1.10 (5 – 9)	1.191•	0.241	NS

Table 4, shows that there was no statistically significant difference found between Enoxaparin group and Rivaroxaban group regarding DVT at 1 month and at 3 month but with higher incidence of DVT at 3 months in Enoxaparin group (10%) than Rivaroxaban group (5%). In comparison the difference between the 2 groups was statistically insignificant.

Table (4): Follow up

Follow up by duplex		**Enoxaparin group**	**Rivaroxaban group**	**Test value**	**P-value**	**Sig.**
		No. = 20	**No. = 20**			
1 month	No DVT	19 (95.0%)	19 (95.0%)	0.000*	1.000	NS
	Yes	1 (5.0%)	1 (5.0%)			
3 months	No DVT	18 (90.0%)	19 (95.0%)	0.360*	0.548	NS
	Yes	2 (10.0%)	1 (5.0%)			

DISCUSSION

DVT is a challenging problem after bariatric surgery but there are few randomized controlled trials studying prophylaxis against DVT in this population. Most bariatric surgery patients carry multiple risk factors for DVT and therefore are at least at moderate risk for suffering DVT in the postoperative period. Although there is an elevated risk, the incidence of postoperative DVT is low. A meta-analysis of 19 studies with 3991 patients demonstrated a weighted mean incidence of PE of 0.5% with fixed prophylactic doses and an incidence of symptomatic DVT of 0.6% with chemoprophylaxis given according to weight [(4)]. Postoperative mortality is frequently caused by PE in the bariatric surgery population [(5)]. The risk of developing DVT is lower at laparoscopic surgery when compared with open bariatric surgery patients (0.34% versus 1.54%) [(6)].

Various strategies have been used to prevent DVT in patients undergoing bariatric surgery, including pharmacologic and mechanical approaches. However, the optimal approach remains unclear. Based on the ACCP guidelines, LMWH, unfractionated heparin, or mechanical prophylaxes with Intermittent Pneumatic Compression (IPC) are recommended. There is no consensus on the standard of care for chemo-prophylactic agent, dosing, timing, or duration. Dosing of pharmacologic prophylaxis is challenging in postsurgical bariatric surgery patients because dosing by body weight may cause excessive anticoagulation and lead to bleeding. Some studies use anti-factor Xa levels to measure adequacy of anticoagulation, but therapeutic levels do not necessarily predict a reduction in DVT. The ACCP guidelines recommend consulting with a pharmacist to determine dosing in obese patients [(7)].

On reviewing the literature for studies comparing different modalities for chemoprophylaxis against VTE in bariatric surgery patients, we did not find any study comparing Enoxaparin and Rivaroxaban prophylactic doses in postsurgical bariatric surgery patients. However, there were multiple studies comparing the efficacy of prophylaxis with both drugs in orthopaedic surgery. Our study is concerned with comparing the efficacy of prophylactic doses of Enoxaparin against the efficacy of prophylactic doses of Rivaroxaban for prevention of VTE in postsurgical bariatric surgery patients.

In our study we compared the efficacy of prophylactic doses of Enoxaparin and Rivaroxaban against DVT in patients undergoing bariatric surgery. While ***Lassen et al.*** [(10)] compared the efficacy of both drugs prophylactic doses in total knee arthroplasty (TKA), and ***Eriksson et al.*** [(11)], compared the efficacy of prophylactic doses of the same drugs after hip arthroplasty (HA).

In our study the a age of assigned patients ranged from 18 to 65 years old with the mean age slightly higher in Rivaroxaban group than Enoxaparin group, the number of females was slightly higher in Rivaroxaban group also. However, the mean BMI was higher in Enoxaparin group "P values were insignificant in the three categories. In one study, Demographic and surgical characteristics were similar between the two groups [(11)]. While in another study, the demographic data Baseline characteristics were well balanced between the two groups except for a slight excess of women in the Rivaroxaban group "P = 0.03" [(10)].

Forty three patients enrolled in our study from which we excluded 3 for presence of previous DVT before surgery or did not come for the scheduled follow up, the remaining 40 patients were divided in 2 double blinded groups "20 patients each" to receive either oral Rivaroxaban 10 mg tablets once daily to be started 12 hours after surgery, or Enoxaparin in a dosage of ½ mg/kg injection (maximum of 80 mg/kg daily) S.C once daily around 12 hours after surgery.

Other RCT study enrolled 2556 patients from which 25 patients were excluded from the study due to failure of screening, the remaining patients were divided in 2 double blinded groups who received same prophylactic dose of Rivaroxaban but initiated 6-8 hours after wound closure, and a different dose of 40mg injection S.C of Enoxaparin once to be started 12 hours before surgery then 6-8 hours after wound closure to be continued once daily after surgery, in this study all patients underwent TKA [(10)].

Another study assigned 4591 patients with 50 patients were excluded according to the exclusion criteria of the study, the remaining patients also were divided in to 2 groups with the same drug regimens of ***Lassen et al.*** [(10)] study except that the

patients of this study underwent hip arthroplasty [11].

The duration of therapy in our study was the same. Patients received the 2 drugs for 14 days in both groups. In one study, the mean duration of prophylaxis was 33.4 days in the Rivaroxaban group and 33.7 days in the Enoxaparin group [11]. In another study, the mean duration of therapy was 11.9 days with rivaroxaban and 12.5 days with enoxaparin [10].

Follow up of our patients was scheduled after one month of undergoing the bariatric surgery and after passing 3 months by venous duplex in our study.

In one study, the follow up was divided into primary efficacy outcome "patients who developed DVT or PE in the 1st 13 to 17 days" where patients were checked 11 to 15 days after surgical procedure, other efficacy outcome checked the incidence of symptomatic or suspected DVT or PE which was investigated by means of bilateral venography or ultrasonography in case of DVT and ventilation- perfusion scintigraphy of the lung, chest radiography & pulmonary angiography [10].

In another study, mandatory bilateral CT venography the day after the last dose of the study drug was done, at 36 days (range, 30 to 42). No further study medication was given after venography. However, further thromboprophylaxis was continued to be given at the investigator's discretion. A follow-up visit was scheduled 30 to 35 days after the last dose of the study drug [11].

On doing follow up venous duplex after one month for the 2 groups of our patients, a single patient developed common femoral DVT in the Rivaroxaban group (5%) also one patient developed ileo-femoral DVT in the Enoxaparin group (5%) with no statistically significant difference between the 2 groups. On 3 months follow up duplex, another new patient developed common femoral DVT in the Enoxaparin group making them total of 2 patients developed DVT through the duration of the study in the Enoxaparin group (10%) and a single patient only in the Rivaroxaban group (5%) in which the difference between the 2 groups was statistically insignificant.

However, in a study the primary efficacy outcome occurred in 79 of 824 patients (9.6%) who received Rivaroxaban, while in the group who received Enoxaparin it occurred in 166 of 878 patients (18.9%). Concerning major venous thromboembolism, it occurred in 9 of 908 patients (1.0%) given Rivaroxaban and 24 of 925 (2.6%) given Enoxaparin. Symptomatic events were less frequent with Rivaroxaban than with Enoxaparin which was statistically insignificant (P value 0.005) [10].

In another study, the primary efficacy outcome occurred in 18 out of 1595 patients (1.1%) in those who received Rivaroxaban, while it occurred in 58 of 1558 patients (3.7%) in the group who received Enoxaparin. Concerning major venous thromboembolism, it occurred in 4 out of 1686 patients (0.2%) in those who received Rivaroxaban, while in Enoxaparin group it occurred in 33 of 1678 patients (2.0%) [11].

Concerning the incidence of bleeding, there was no incidence of surgical wound or intra-abdominal bleeding reported postoperatively and during the follow up period through our whole study.

A study reported major bleeding occurred in 0.6% of patients in patients who received Rivaroxaban, while it occurred in 0.5% of the group who received Enoxaparin [10].

Another study reported that major bleeding occurred in 6 of 2209 patients (0.3%) who received Rivaroxaban, while occurred only in 2 of 2224 patients (0.1%) who received Enoxaparin (P = 0.18) [11].

CONCLUSION

From the previous results, further Randomized Controlled studies should be done on a larger cohort of patients undergoing bariatric surgery to determine the efficacy and to set new guidelines for DVT prophylaxis in bariatric patients bearing in mind terms of efficacy, safety and compliance on therapeutic regimens.

REFERENCES

1. Colquitt JL, Pickett K, Loveman E, et al. Surgery for weight loss in adults. Cochrane Database Syst Rev. 2014; 8: CD003641.
2. Ashrafian H, Toma T, Rowland SP, et al. Bariatric Surgery or Non-Surgical Weight Loss for Obstructive Sleep Apnoea? A Systematic Review and Comparison of Meta-analyses. Obes Surg. 2015; 25: 1239–1250.

3. Stein PD and Matta F. Pulmonary embolism and deep venous thrombosis following bariatric surgery. Obes Surg. 2013; 23(5): 663–668.
4. Becattini C, Agnelli G, Manina G, et al. Venous thrombo-embolism after laparoscopic bariatric surgery for morbid obesity: clinical burden and prevention. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2012; 8(1): 108-15.
5. Morino M, Toppino M, Forestieri P, et al. Mortality after bariatric surgery: analysis of 13,871 morbidly obese patients from a National Registry. Ann Surg. 2007; 246(6): 1002–1007.
6. Winegar DA, Sherif B, Pate V, et al. Venous thromboembolism after bariatric surgery performed by Bariatric Surgery Centre of Excellence Participants: analysis of the Bariatric Outcomes Longitudinal Database. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2011; 7(2): 181-8.
7. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2): e227S-77S.
8. Li W, Gorecki P, Semaan E, et al. Concurrent prophylactic placement of inferior vena cava filter in gastric bypass and adjustable banding operations in the Bariatric Outcomes Longitudinal Database. J Vasc Surg. 2012; 55(6):1690-5.
9. Kaw R, Pasupuleti V, Wayne Overby D, et al. Inferior vena cava filters and postoperative outcomes in patients undergoing bariatric surgery: a meta-analysis. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2014; 10(4): 725-33.
10. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med, 2008; 358(26): 2776-2786.
11. Ericsson BI, Borris LC, Friedman RJ, et al. Study Group Rivaroxaban versus enoxaparin for thromboprophylaxisd after hip arthroplasty. N Engl J Med, 2008; 358(26): 2765-2775.