

Oral rivaroxaban for postoperative prophylaxis of venous thromboembolism after sleeve gastrectomy in patients with morbid obesity, is it safe: A prospective randomized clinical trial

Original
Article

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ABSTRACT

Background: Deep vein thrombosis and pulmonary embolism are still one of the most crucial problems after weight-reducing surgeries in patients suffering from obesity. Many techniques were documented and routinely applied to prevent venous thromboembolism (VTE), particularly in those who are at high risk as morbid obese patients (BMI >40 kg/m²), geriatric patients, and those who had previous history of VTE and open or revisional surgery.

Patients and Methods: We conducted this randomized prospective clinical trial during the period from January 2021 to January 2023 on 500 obese patients who underwent sleeve gastrectomy for weight reduction divided into two groups: In the 250 patients of group A we used postoperative low-molecular-weight heparins (LMWH) 40 mg once daily subcutaneous injection for VTE prophylaxis, while group B (250 patients) were given oral anticoagulants (rivaroxaban) on the other hand.

Results: This study aimed to compare the results of using both drugs as regards complications including both VTE and bleeding. Regarding bleeding, it also can present with a wide range of manifestations ranging from mild symptoms like port site hematoma, perigastric hematoma, or hematemesis, and melena.

Regarding the age of patients in the studied groups there was no statistically significant difference between both groups. The incidence of minor, moderate to major, and life-threatening bleeding was nearly the same between both groups with no statistically significant difference. Throughout the study, only one case of porto-mesenteric thrombosis in the LMWH group. No clinically suspected Lower Limb deep vein thrombosis throughout the study with no need to do lower limb venous duplex.

Conclusion: The safety and efficacy of Rivaroxaban as one of the most commonly used new Oral anticoagulants resembles that of the LMWH as a prophylaxis of VTE following weight-reducing sleeve gastrectomy surgery and could be a good oral alternative for LMWH.

Key Words: Rivaroxaban, sleeve, thrombosis.

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INTRODUCTION

Obesity, now one of the most common worldwide health problems represents a medical, social, and economic burden^[1-3]. Bariatric surgeries now are the most successful and longstanding method of weight reduction and obesity-related comorbidities management, but unfortunately, as one of the most common postoperative complications, the risk venous thromboembolism (VTE) especially increases after bariatric surgeries^[4]. This strong association between VTE and bariatric surgeries and also obesity itself as a VTE development independent risk factor is well settled^[5-7].

Deep-venous thrombosis (DVT) may affect any one of the large veins, especially those of the lower limbs (LL) typically presenting with pain, tenderness, and swelling^[8].

VTE related morbidity and mortality, together with its social and economic burden makes the prophylaxis and treatment of it a major concern facing the health care providers^[9].

The increasing rates of performed Laparoscopic sleeve gastrectomies (LSG) in recent years reflect its great success in controlling obesity and its associated comorbidities^[10].

One of the most serious forms of VTE is the thrombosis of the Porto-mesenteric vein (PMVT) that although it is rare, but associated with more morbidity and mortality^[11] presenting with abdominal pain and fever in most cases^[12]. Some cases of PMVT are asymptomatic and are discovered accidentally during radiological examination^[10].

PMVT may complicate other abdominal surgeries, not only LSG, like Neissen's fundoplication, splenectomy, and cholecystectomy^[13,14].

The reason why PMVT may complicate laparoscopic surgeries especially LSG, is not well known. That is why the exact etiology is still not clearly understood. The high intra-abdominal pressure following abdominal insufflation causes decreasing blood flow within the portal vein, the Vasopressin release as a result of surgical stress, and the patient intraoperative in reverse Trendelenburg positioning were supposed to be the initiating factors^[15].

DVT occurrence rate could not be calculated adequately as symptomatic DVT and symptomatic pulmonary embolism incidence is only about 5.4 and 6.4% of postoperative cases^[15].

The high incidence of VTE indicates that aggressive prophylaxis is needed to prevent it^[16-18], especially after bariatric surgery recommended by the American Society of Metabolic and Bariatric Surgeons and also the American College of Chest Physicians recommended aggressive prophylaxis against VTE in obese surgical candidate patients^[19].

Many measures are now well settled to help VTE prevention including intermittent pneumatic compression, Perioperative use of low-molecular-weight heparins (LMWHs), and patient early mobilization after surgery^[18,20].

Although the presence of known consensus regarding LMWH dose, timing, and duration in the field of bariatric surgery, many Physicians lack using it in their clinical practice^[20]. Postsurgical VTE occurrence timing is variable, but mostly within 30 days after surgery, so, prolonged prophylaxis against VTE should be considered in high-risk patients^[17].

The new application generation of direct oral anticoagulants (DOACs) in VTE prophylaxis has been met with great compliance in contrast to the commonly used LMWH because of their effectiveness and safety without the need for continuous monitoring.

Rivaroxaban as the first published oral direct-factor Xa inhibitor is now well known to many physicians who initially used it for the prophylaxis of VTE after elective hip- and knee-replacement surgery^[21,22].

Rivaroxaban is well tolerated, rapid onset, and long-acting anticoagulant with a high oral bioavailability (80–100%) over 24 h reaching its maximum plasma level after 2–4 h and not affected by food^[21,22].

Aim/objective

To assess the effectiveness and safety of rivaroxaban as an oral anticoagulant in contrast to the commonly used LMWH in the prophylaxis of VTE after sleeve gastrectomy's in morbid obese patients.

PATIENTS AND METHODS:

This study is a prospective randomized clinical trial that was conducted on 500 obese patients Who underwent sleeve gastrectomy (the number is determined by power calculation) presenting to General Surgery Department, Tanta University Hospital during the period from Jan to Dec 2023.

The patients were randomized into one of the two following groups by sealed envelope technique:

(a) Group A (250 patients) received rivaroxaban 10 mg once daily for 30 days starting just after the day of surgery.

(b) Group 2 (250 patients) received 40 mg subcutaneous LMWH injection (clexane) once daily for 30 days starting just after the day of surgery.

Ethical approval was obtained from the Research Ethical Committee of the Faculty of Medicine, Tanta University.

Inclusion criteria

(a) Age 18–60 years old.

(b) Morbid obese patients with BMI greater than or equal to 40 kg/m² or more than 30 with comorbidities (e.g. hypertension and/or diabetes mellitus).

Exclusion criteria

We excluded patients with a history of previous bariatric surgeries, those patients converted to open technique due to intraoperative adverse events, pregnant or lactating females, patients with psychiatric disorders, patients with contraindications to anticoagulation, such as recent cerebral hemorrhage, or coagulopathy, patients with known allergy to the studied drugs and patients with major postoperative complications as reactionary bleeding or leakage.

Technique

After surgery, all patients in both study groups started clear fluids the night of surgery together with adequate intravenous fluids, and were encouraged for early mobilization. Group A started rivaroxaban 10 mg once daily for 30 days starting 24 h after surgery while group B started 40 mg LMWH subcutaneous injection once daily for 30 days starting 24 h after surgery.

WHO classified postoperative bleeding severity into 4 grades as the following: grade 0=no bleeding, grade 1=petechial bleeding, grade 2=mild blood loss (clinically significant), grade 3=gross blood loss, requiring transfusion (severe), grade 4=debilitating blood loss, retinal or cerebral associated with fatality^[23].

The bleeding management strategy for our patients in need of blood transfusion involves the recommendations of the recent AABB International Guidelines for blood transfusions and the ATLS guidelines for management of hypovolemic shock^[24,25].

We recorded any cases with any form of postoperative bleeding and any detected cases of suspected VTE.

Complete blood count, pelvi-abdominal were routinely done in all cases.

Computed tomography (CT) abdomen with intravenous contrast was done only in clinically suspected cases where u/s was inconclusive or when u/s showed suspected intra-abdominal collection.

Suspected cases of LL DVT were evaluated using duplex u/s, while those with suspected portal vein thrombosis were evaluated using CT abdomen with intravenous contrast.

The endpoint of our study was the incidence of postoperative VTEs or hemorrhage.

RESULTS:

Each of the studied groups included 250 patients, with a mean age of about 34 years in group A (rivaroxaban) and about 35 years in group B (LMWH). There was female predominance in group B, with a statistically significant difference between the two groups. Associated co-morbidities were found in 70 patients in group A, in contrast to only 52 patients in group B with statistically significant difference between the two groups. There was no difference in statistical significance between the two groups regarding BMI (Table 1).

Although there was only a mild difference between the two groups regarding the operative time and the postoperative hospital stay, it was statistically significant (Table 2).

Table 1: Demographic data of the studied groups

	LMWH (N=250) [n (%)]	Rivaroxaban (N=250) [n (%)]	Test of Significance	P
Age				
Mean±SD	35.7±7.2	34.4±6.41	U=28325.0	0.070
Median (min–max)	34.5 (24.0–51.0)	34.0 (23.0–51.0)		
Sex				
Male	85 (34.0)	125 (50.0)	$\chi^2=13.136^*$	<0.001*
Female	165 (66.0)	125 (50.0)		
Comorbidities				
No	198 (79.2)	180 (72.0)		
Asthmatic	16 (6.4)	20 (8.0)	$\chi^2=20.482^*$	<0.001*
Diabetic	16 (6.4)	40 (16.0)		
Hypertensive	20 (8.0)	10 (4.0)		
BMI				
Mean±SD	45.02±3.43	44.54±3.37	t=1.551	0.122
Median (min–max)	45.0 (40.0–50.0)	44.0 (40.0–50.0)		

χ^2 , Chi square test; FE, Fisher Exact; MC, Monte Carlo; SD, Standard deviation; t, Student t test; U, Mann–Whitney test.

P: P value for comparing between the two studied groups

*: Statistically significant at P less than or equal to 0.05.

Table 2: Operative data

	LMWH (N=250) [n (%)]	Rivaroxaban (N=250) [n (%)]	Test of Significance	P
Operative time				
Mean±SD	87.40±12.84	82.44±13.18	U=24290.0*	<0.001*
Median (min–max.)	90.0 (65.0–110.0)	80.0 (65.0–110.0)		
Hospital stay in days				
1	200 (80.0)	160 (64.0)	$\chi^2=15.873^*$	<0.001*
2	50 (20.0)	90 (36.0)		

Seven female cases in both groups, had menorrhagia that were managed conservatively by only stopping the anticoagulant during menses and completing their doses later on. None of them showed marked decrease in red blood cells (RBCs) count nor hemoglobin concentration needing a blood transfusion.

Port site subcutaneous hematoma was found in 63 cases in both groups without statistically significant difference, which were managed conservatively by topical application of recombinant hirudin and oral amoxicillin for prevention of bacterial infection. None of them showed marked decrease in RBCs count or hemoglobin concentration needing a blood transfusion.

Two cases in the LMWH group and one in the rivaroxaban group had perigastric hematoma discovered in pelvi-abdominal CT after ultrasound suspicion of perigastric collection after 14 days postoperatively that were managed conservatively only by stopping the anticoagulant without a marked decrease in RBCs count nor hemoglobin concentration needing a blood transfusion and was followed-up regularly every 2 weeks for 2 months by ultrasound that showed gradually regressive course regarding the size, except for one case that had associated

hematemesis and melena and needed transfusion of two units of packed RBCs, stoppage of anticoagulant, fresh frozen plasma transfusion (Table 3). After successful conservative control, there was no need for urgent esophagogastroscopy, but later on – 3 months after the operation- esophagogastroscopy was done that was free.

Only 1 case in the LMWH group presented 20 days after the operation with severe abdominal pain, mild grade fever and vomiting. Ultrasonography showed portal vein thrombosis that was confirmed by CT abdomen showing near total occlusion of the portal vein. The patient was admitted in the ICU and managed conservatively by I.V fluids, liver support, and therapeutic doses of LMWH (80 mg, twice daily) and was discharged home after 10 days. After 6 months, the patient presented with manifestations of subacute small bowel obstruction. CT abdomen showed mechanical obstruction with a mid-jejunal transition zone. The patient was explored and we found jejunal stricture about 100 cm from the duodeno-jejunal junction that was resected followed by bowel anastomosis.

No cases of LL DVT occurred in any of the studied groups.

Table 3: Incidence of postoperative hemorrhage and portal vein thrombosis

	LMWH (N=250) [n (%)]	Rivaroxaban (N=250) [n (%)]	Test of Significance	P
Minor bleeding				
No	221 (88.4)	209 (83.6)		
Menorrhagia	3 (1.2)	4 (1.6)	$\chi^2=2.438$	^{MC} P=0.292
Port site hematoma	26 (10.4)	37 (14.8)		
Moderate to major bleeding				
No	248 (99.2)	249 (99.6)	$\chi^2=0.335$	^{FE} P=1.000
Perigastric hematoma	2 (0.8)	1 (0.4)		
Life threatening bleeding				
No	249 (99.6)	250 (100.0)	$\chi^2=1.002$	^{FE} P=1.000
Hematemesis and melena	1 (0.4)	0		
Patients needing blood transfusion	1 (0.4)	0	$\chi^2=1.002$	^{FE} P=1.000
Hematoma in U/S	2 (0.8)	1 (0.4)	$\chi^2=0.335$	^{FE} P=1.000
LL DVT	0	0	–	–
Portal vein thrombosis	1 (0.4)	0	$\chi^2=1.002$	^{FE} P=1.000
Pulmonary embolism	0	0	–	–

χ^2 , Chi square test; FE, Fisher Exact; MC, Monte Carlo; SD, Standard deviation; t, Student t test; U, Mann–Whitney test.
P: P value for comparing between the two studied groups *: Statistically significant at P less than or equal to 0.05

DISCUSSION

In this randomized controlled clinical trial, we examined the successful pharmacologic thromboprophylaxis effect of two widely applicable drugs after LSG surgery, the new oral anticoagulant group namely, rivaroxaban and the famous classically used low molecular weight heparin.

Many prestigious societies concerning either obesity as a worldwide problem or bariatric and metabolic surgery as a long-lasting management of this problem or even those who are interested in VTE prophylaxis rather than its treatment with its all catastrophic comorbidities, like the American Association of Clinical Endocrinologists guidelines, the American Society for Metabolic and Bariatric Surgery Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic and Nonsurgical Support of the Bariatric Surgery Patient, and Obesity Society (AACE/ASMBS/TOS guidelines) recommended that not only the regular use of intermittent pneumatic compression appliances is enough for VTE prophylaxis after weight reducing surgeries, but also, extended prophylaxis using either those well-known LMWH or the unfractionated heparin should be considered^[26]. This routine anticoagulation is now the cornerstone of VTE prophylaxis after bariatric surgery that is universally applied by most of surgeons.

For many years, the surgeons used either LMWH or unfractionated heparin for VTE prophylaxis after bariatric surgeries; as of now, there is no consensus regarding the type of heparin, its dose, and for how long the prophylaxis of VTE postoperatively is needed^[27].

One study documented that only a 10 days prophylaxis duration using heparin is adequate and safe after bariatric surgery^[28]. Others demonstrated that although preoperative LMWH prophylaxis was associated with a significant rate of intraoperative bleeding without the expected success rate of postoperative VTE prophylaxis, its postoperative dose was efficient^[29].

Throughout this prospective study, we did not recognize any clinically suspected LL DVT, supporting successful anticoagulation in both groups.

Some studies confirmed even higher efficacy of rivaroxaban versus enoxaparin regarding VTE prophylaxis after hip and knee replacement surgeries with nearly the same incidence of postoperative bleeding^[30–33]. Friedman *et al.*^[34] found in their comparative study regarding the VTE prophylaxis efficacy of rivaroxaban in orthopedic surgery obese patients with different body mass indices (more, equal,

or less than 40 kg/m²) that there was no statistically significant difference in the rates of either VTE or bleeding^[35].

As regards age differences in this study, no statistically significant difference was found between both study groups. Associated co-morbidities were found in 70 patients in group A, in contrast to only 52 patients in group B with statistically significant difference between the two groups. There was no difference in statistical significance between the two groups regarding BMI.

Seven female cases in both groups, had menorrhagia, while port site subcutaneous hematoma was found in 63 cases in both groups without statistically significant difference, and all were managed conservatively without marked decrease in RBC count nor hemoglobin concentration demanding blood transfusion.

As regards moderate-to-major bleeding, 2 cases in the LMWH group and one in the rivaroxaban group had perigastric hematoma discovered in pelvi-abdominal CT after ultrasound suspicion of perigastric collection after 14 days postoperatively that were managed conservatively. Only 1 case in the LMWH group had portal vein thrombosis followed by small bowel stricture necessitating surgical intervention later on.

Recently, some large systematic reviews and meta-analysis studies favor the use of apixaban over rivaroxaban in VTE prophylaxis, claiming a lower incidence of gastrointestinal bleeding than rivaroxaban, but the doubt of these results arose from the fact that these studies were conducted on cardiac patients with long-term oral anticoagulants use history^[36].

Rivaroxaban specifically is marked by its high affinity for plasma protein binding with low tissue affinity, so the drug metabolism is neither affected significantly by the body weight nor the bariatric surgery itself^[37]. As these oral anticoagulant drugs pharmacokinetics are affected largely by the bowel absorption capacity, we excluded bypass surgeries from our study because of the malabsorption limb of that type of operation.

CONCLUSION

Rivaroxaban is a safe and effective alternative to LMWH in the prophylaxis of different VTE forms after sleeve gastrectomy in morbid obese patients.

CONFLICT OF INTEREST

There are no conflicts of interest.

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