

# Is rivaroxaban a safe and effective oral alternative to low-molecular-weight heparin in prophylaxis of portomesenteric and lower-limb deep-vein thrombosis after sleeve gastrectomy?

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## Background

The incidence of symptomatic deep-vein thrombosis (DVT) and pulmonary embolism ranges from 0 to 5.4% and 0 to 6.4%, respectively, but the true incidence remains uncertain. Although the overall incidence is low, venous thromboembolic events (VTE) represents a significant cause of morbidity and mortality after surgery. Even with aggressive prophylaxis, VTE cannot be fully prevented. The American Society of Metabolic and Bariatric Surgeons and the American College of Chest Physicians recommend prophylaxis against DVT for all bariatric surgery patients. Routine prophylactic perioperative use of low-molecular-weight heparins (LMWHs), intermittent pneumatic compression devices, and early mobilization are currently the major accepted measures to prevent VTE, particularly in high-risk groups (BMI >50 kg/m<sup>2</sup>), advanced age, history of previous VTE, obesity hypoventilation syndrome, and open and revisional surgery.

## Patients and methods

This prospective randomized clinical trial conducted on all obese patients underwent sleeve gastrectomy during the period from January 2018 to June 2020 (600 patients) with follow-up till January 2021. The patients were randomized into two groups with sealed-envelope technique, group 1 (300 patients) was given LMWH in prophylaxis of VTE. Group 2 (300 patients) was given direct oral anticoagulants (rivaroxaban) in prophylaxis of VTE.

## Results

In our study, we compared between both groups as regards the incidence of complications among both groups, bleeding grade, recorded cases of hemoglobin drop during follow-up complete blood count, and any detected cases of abdominal bleeding or perigastric hematoma, and any detected cases of DVT in lower-limb (LL) venous duplex. There was no significant difference between both study groups as regards age. Minor bleeding was statistically higher among group-2 (13.3%) compared with group-1 (0.3%) cases. Moderate-to-major bleeding was statistically higher among group-1 (4%) compared with group-2 cases (0.3%). However, there were no statistically significant difference between both study groups as regards life-threatening bleeding. Throughout the study, no detectable portomesenteric vein occlusion or thrombosis in routine ultrasound was done 3 days postsleeve gastrectomy even if the patient is not complaining. No clinically suspected LL DVT throughout the study with no need to do LL venous duplex.

## Conclusion

Rivaroxaban is a safe and effective alternative to LMWH in prophylaxis of portomesenteric and LL DVT after sleeve gastrectomy with better compliance and more patient satisfaction to the oral alternative.

## Keywords:

anticoagulation, rivaroxaban, sleeve, thrombosis

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## Introduction

Worldwide prevalence of obesity is increasing in addition to socioeconomic and medical burden [1–3]. Reduction of weight and comorbidities are mostly sustainably reduced by bariatric surgeries, but bariatric surgery increases the venous thromboembolic event (VTE) risk [4].

The association between VTE and obesity after bariatric surgery is established well in studies in

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addition to the strong association between obesity itself as an independent risk factor for VTE development [5–7].

Deep-venous thrombosis (DVT) is formation of blood clots in one of the large veins, the lower limbs (LL) commonly. It may lead to partial or complete block of circulation in that vein, it may lead to pain, tenderness, swelling, and skin warmth and discoloration [8].

Prevention of thromboembolic events and treatment are major health concerns in the aspect of the risk of excess mortality, the socioeconomic impact, and medical issues increase the concern by this pathology [9].

Laparoscopic sleeve gastrectomy (LSG) is increasingly offered for patients with morbid obesity. LSG assists in weight loss and reduces comorbidities and improves quality of life [10].

Portomesenteric vein thrombosis (PMVT) is a rare but serious complication that may follow LSG. PMVT occurs when partially or entirely the portal or mesenteric veins are occluded by a thrombus [11].

Migration of the thrombus to obliterate portal vein branches, splenic, and mesenteric veins may follow the formation of the thrombus at one of these veins. Various clinical manifestations, such as abdominal pain and fever, may be the presentation [12].

Although PMVT is a lethal complication in the postoperative course of LSG, the diagnosis is very misleading. Abdominal pain or slight discomfort, nausea, pyrexia, or vomiting may be the presentation of this complication. Some PMVT cases are asymptomatic, and during radiological examination, are discovered accidentally [10].

PMVT was not only reported after LSG, but also has been reported following various laparoscopic procedures, for example, cholecystectomy, splenectomy, and Neissen's fundoplication [13,14].

The exact etiology is still not clearly understood. Experimental studies found that abdominal insufflation and intraabdominal pressure has an inverse relation to blood flow within the portal vein, which is the nidus for preparation of thrombus formation. Vasopressin release during surgery, reverse Trendelenburg position, and increased portal venous pressure due to carbon dioxide retention may be also contributing factors [15].

The true incidence of DVT remains uncertain as symptomatic DVT incidence is about 5.4% and symptomatic pulmonary embolism incidence is about 6.4% [15].

VTE is a leading cause of morbidity and mortality following surgery. VTE cannot be prevented adequately even with aggressive prophylaxis. This is although its incidence is low [16–18].

It is recommended by the American Society of Metabolic and Bariatric Surgeons and the American College of Chest Physicians to give prophylaxis against DVT for all patients who will undergo bariatric surgery [19].

Perioperative prophylactic low-molecular-weight heparins (LMWHs), intermittent pneumatic compression, and encouraging early mobilization are the major accepted measures to prevent VTE, especially in high-risk patients [18,20].

Physicians lack consensus supporting their therapeutic decisions in clinical practice as regards LMWH dose, timing, and duration in the field of bariatric surgery [20].

VTE events may occur within 30 days after surgery, so, extended VTE prophylaxis should be considered, but the duration of chemical prophylaxis after surgery is still controversial [17].

Direct oral anticoagulants (DOACs) are a new generation of anticoagulants, whose application is more convenient compared with LMWH with great compliance. Effective and safe anticoagulation and no need for monitoring are the most important advantages of DOACs. Rivaroxaban is the first marketed oral direct-factor Xa inhibitor. It was initially approved for the prevention of VTEs after elective hip- and knee-replacement surgery [21,22].

Rivaroxaban is well tolerated and a predictable dose-dependent pharmacology profile up to 24 h after single-dose application is well demonstrated. The 10-mg dose of rivaroxaban has a high oral bioavailability (80–100%), irrespective of food intake, a rapid onset of action, and the maximum plasma level is achieved 2–4 h after oral administration [21,22].

#### **Aim/objective**

To compare the efficacy and safety of DOAG (rivaroxaban) versus LMWH in prophylaxis of DVT of portomesenteric and LL veins for morbid obese patients who underwent sleeve gastrectomy.

## Patients and methods

This prospective randomized clinical trial involved 600 obese patients conducted at Ain Shams University Hospitals, Al-Hurria Hospital and Weqaya Specialized Hospital during the period from January 2018 to January 2020 with follow-up till June 2020. The patients were divided into two groups by sealed-envelope technique, group 1 (300 patients) were given rivaroxaban 10 mg once daily for 14 days postoperative starting from the next day of surgery. Group 2 (300 patients) were given LMWH (clexane) 40 mg of subcutaneously injection once daily for 14 days postoperative starting from the next day of surgery.

Ethical approval was taken from the Ain Shams University, Faculty of Medicine, General Surgery Department Research Ethical committee No. IRB 0006379 and written consent was taken from every patient after explanation of all details, advantages, disadvantages, realistic expectations, and all the possible early and late postoperative complications. Surgeries were done by the same surgical team throughout the study with the same technique.

### Inclusion criteria

We included obese male or female patients aged from 18 to 60 years with BMI more than 35 or more than 30 with comorbidities (e.g. hypertension and/or diabetes mellitus).

### Exclusion criteria

We excluded from the study the patients who underwent one anastomosis gastric bypass, patients who had previous bariatric surgeries, when laparoscopic sleeve was converted to open sleeve, pregnant or lactating women, patients with psychiatric disorders, patients with contraindication to anticoagulation, such as recent cerebral hemorrhage, active bleeding, coagulopathy, thrombocytosis, known allergy to study drugs, known protein C, protein S, and antithrombin III deficiency. Patients who developed surgical complications, such as bleeding in the first 24 h after surgery, which required surgical interventions, were excluded from the study.

### Technique

After surgery, in both study groups, intermittent pneumatic compression and early mobilization were applied as standard of care and ensure adequate intravenous fluids as thrombosis prophylaxis to maintain blood viscosity within the normal range, till the oral fluids were allowed 12 h after surgery. In group 1 (LMWH group) LMWH was started

postoperatively 24 h after closure of the surgical site, provided stable hemostasis had been achieved. Patients with BMI less than 50 kg/m<sup>2</sup> received 40 mg of subcutaneous enoxaparin (clexane), those with BMI more than or equal to 50 kg/m<sup>2</sup> received 60 mg. In contrast, the other group (rivaroxaban group) was given rivaroxaban 10 mg once daily 24 h after surgery. Both groups were given anticoagulation for 14 postoperative days. Both groups were given proton-pump inhibitors for 2 months postoperatively.

We compared between both groups as regards the incidence of complications among both groups, bleeding grade according to the WHO classification, which made a standardized grading scale to measure the severity of bleeding 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], recorded cases of hemoglobin drop during follow-up complete blood count (CBC), any detected cases of abdominal bleeding or perigastric hematoma, and any detected cases of DVT in LL venous duplex.

The endpoints of our study were the eventless postoperative period with no VTEs (the first postoperative month) or the occurrence of surgical complications such as hemorrhage where reoperation was needed or the conversion of the laparoscopic procedure to open surgical technique.

## Results

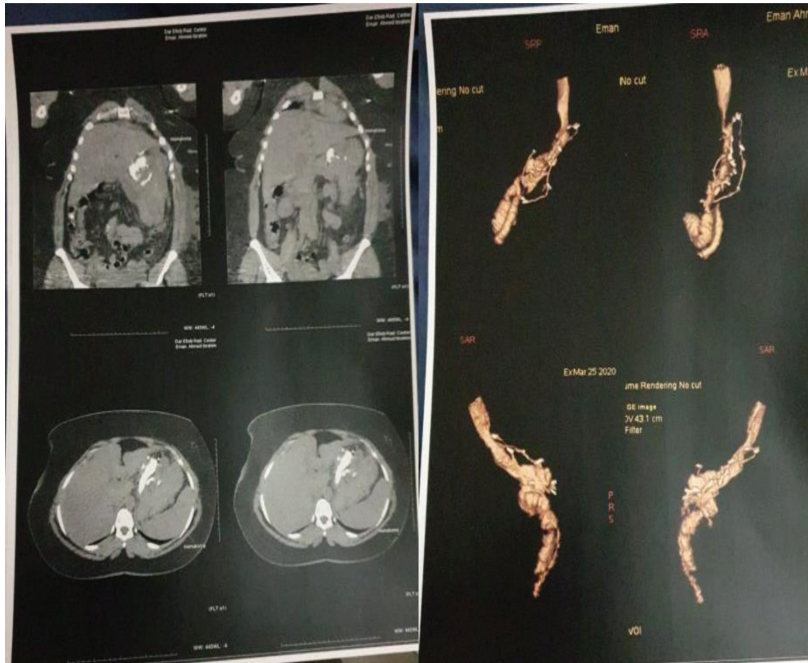
In group 1 (LMWH group), 12 cases have had a perigastric hematoma postsleeve gastrectomy discovered in pelviabdominal computed tomography (CT), two of them have had an ultrasound (U/S) finding of collection around the stomach (Fig. 1, Tables 1 and 2).

In group 2 (Rivaroxaban Group), petechial bleeding occurs in 40 cases of rivaroxaban group (Fig. 2, Table 3).

There was no significant difference between both study groups as regards age. Minor bleeding was statistically higher among group-2 (13.3%) compared with group-1 cases (0.3%). Moderate-to-major bleeding was statistically higher among group-1 (4%) compared with group-2 cases (0.3%) (Fig. 3). However, there were no significant differences between both study groups as regards life-threatening bleeding (Tables 4 and 5).

There was no significant difference between both study groups as regards life-threatening bleeding,

Figure 1

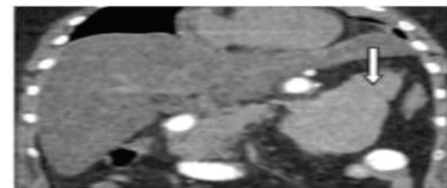


CT Abdomen & Pelvis  
Post bariatric surgery protocol with 3D Volumetry

- **Free flow** of contrast via the oesophagus, sleeved stomach and small bowel with **no** evidence of contrast hold up or leakage/extravasation beyond the sleeved stomach boundaries.
- Increased angulation of the sleeved stomach is noted at the level of incisura angularis .
- Well defined hyperdense **perigastric two collection** are seen. The largest measures about 2.2 x 3.5 x 2.3 cm, picture is impressive of pergastric hematomas.
- **Normal** diameter of the small bowel loops with no evidence of small bowel obstruction.
- **No** hiatus hernia is demonstrated.
- **No** free fluid could be detected.

CT Abdomen & Pelvis  
Post bariatric surgery protocol with 3D Volumetry

- **Free flow** of contrast via the oesophagus, sleeved stomach and small bowel with no evidence of contrast hold up or extravasation beyond the sleeved stomach boundaries.
- Large well defined hyperdense **perigastric hematoma** is seen, measuring about 14 x 13.5 x 15.2 cm. **No evidence** of sleeved stomach compression or luminal narrowing
- **Normal** diameter of the small bowel loops with no evidence of small bowel obstruction.
- **No** free fluid could be detected.
- Bilateral lower lobe atelectatic bands are seen. No pleural effusion



Perigastric hematoma post sleeve gastrectomy in pelviabdomina CT in LMWH group some cases.

hemoglobin drop on follow-up CBC, and follow-up U/S. No detectable PMVT in routine U/S was done 3 days postsleeve gastrectomy even if the patient is not complaining. No clinically suspected LL DVT throughout the study with no need to do LL venous duplex.

### Discussion

In this trial of pharmacologic thromboprophylaxis after LSG surgery, treatment was given with rivaroxaban, an orally active direct inhibitor of factor Xa.

American Association of Clinical Endocrinologists (2013) 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 intermittent pneumatic compression devices and LMWH and unfractionated heparin after bariatric surgery for VTE prophylaxis. A long period (extended prophylaxis) should be considered for high-risk patients [24].

Prophylactic anticoagulation routinely administered after bariatric surgery is universally accepted and suggested by many surgeons. Both LMWH and unfractionated heparin can be used in bariatric surgery; however, till now, no consensus regarding dose, starting point, and duration of prophylactic heparin is established [25].

DVT prophylaxis given for surgical patients can be used in PMVT prophylaxis. One study demonstrated that 10 days of prophylactic heparin administered after bariatric surgery is adequate and efficient [26].

Other studies demonstrated that enoxaparin prophylaxis given preoperatively was associated with a significant

**Table 1 Description of all parameters among group-1 cases (low-molecular-weight heparin group)**

	Mean±SD/n (%)
Age (years)	36.12±12.34
Minor bleeding (petechial bleeding grade 1) [n (%)]	
No	299 (99.7)
Yes	1 (0.3)
Moderate-to-major bleeding (grade 2)	
No	288 (96.0)
Perigastric hematoma in CT	12 (4.0)
Life-threatening bleeding (grade 3)	
No	300 (100.0)
Hematemesis	0
HGB drop on follow-up CBC	
Negative	298 (99.3)
Drop	2 (by about 2 g/dl) (0.7%)
Follow-up U/S	
Normal	298 (99.3)
Perigastric hematoma	2 (0.7)
LL venous duplex	
Clinically negative	300 (100.0)
Pelviabdominal CT if clinically suspected or U/S-positive collection	
Normal	288 (96.0)
Perigastric hematoma	12 (4.0)

CBC, complete blood count; CT, computed tomography; HGB, hemoglobin; LL, lower limb; U/S, ultrasound.

**Table 2 Description of all parameters among group-2 cases (rivaroxaban group)**

	Mean±SD/n (%)
Age (years)	35.01±11.68
Minor bleeding (petechial bleeding grade 1)	
No	260 (86.7)
Yes	40 (13.3)
Moderate-to-major bleeding (grade 2)	
No	299 (99.7)
Perigastric hematoma	1 (0.3)
Life-threatening bleeding (grade 3)	
No	299 (99.7)
Hematemesis	1 (0.3)
HGB drop on follow-up CBC	
Negative	298 (99.3)
Drop	2 (1 by about 6 g/dl, the other by 2 g/dl) (0.7)
Follow-up U/S	
Normal	299 (99.7)
Perigastric hematoma	1 (0.3)
LL venous duplex	
Clinically negative	300 (100.0)
Pelviabdominal CT if clinically suspected or U/S-positive collection	
Normal	299 (99.7)
Perigastric hematoma	1 (0.3)

CBC, complete blood count; HGB, hemoglobin; LL, lower limb; U/S, ultrasound.



Figure 2



Petechial bleeding mostly in wound areas in Rivaroxaban group.

rate of major bleeding without reduction in DVT incidence. It was noticed that 40 mg of enoxaparin given twice daily after surgery is efficient [27].

Throughout the study, no clinically suspected patients for LL vein DVT were detected, so no LL venous duplex was requested supporting that

adequate anticoagulation offered in both groups was adequate.

Our study was conducted to compare the safety and efficacy of rivaroxaban prophylaxis in contrast to LMWH postsleeve gastrectomy for prevention of DVT of portomesenteric and LL veins. So, we

**Table 3 Comparison between study groups as regards clinical data and laboratory investigations-**

	Groups (mean±SD)		P	Significance
	LMWH	Rivaroxaban		
Age	36.12±12.34	35.01±11.68	0.257	NS
	LMWH [n. (%)]	Rivaroxaban [n (%)]		
Minor bleeding (petechial bleeding grade 1)				
No	299 (99.7)	260 (86.7)	0.001	HS
Yes	1 (0.3)	40 (13.3)		
Moderate-to-major bleeding (grade 2)				
No	288 (96.0)	299 (99.7)	0.002	HS
Perigastric hematoma	12 (4.0)	1 (0.3)		
Life-threatening bleeding (grade 3)				
No	300 (100.0)	299 (99.7)	1.0	NS
Hematemesis	0	1 (0.3)		

LMWH, low-molecular-weight heparin. ‡Student *t* test. \* $\chi^2$ . \*\*Fisher's exact test.

**Figure 3**

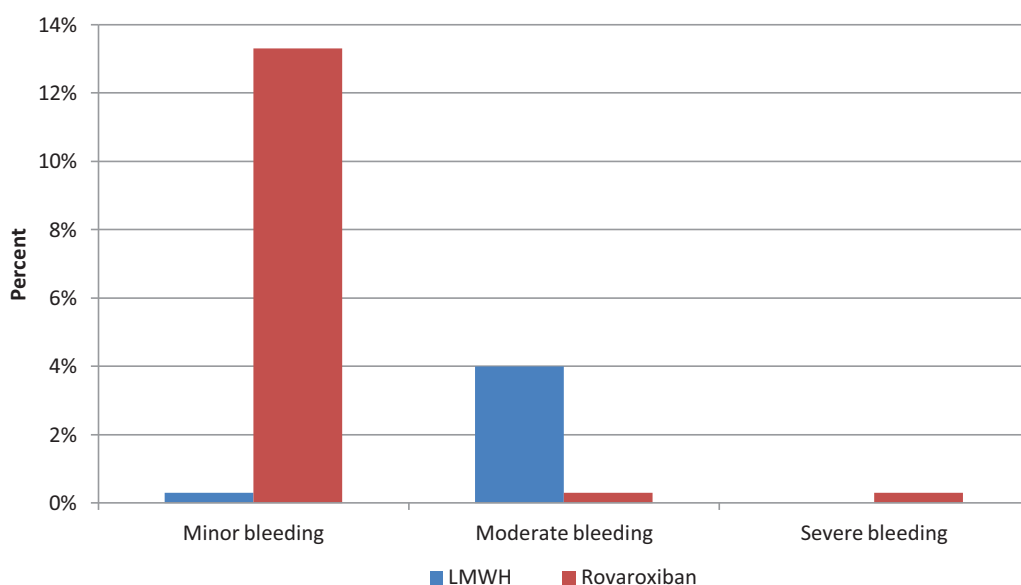


Chart showing comparison of bleeding complications between both groups as regards bleeding degree.

administered LMWH and rivaroxaban prophylaxis for 300 patients.

After hip-replacement and knee-replacement surgery with the same incidence of bleeding as regards VTE prophylaxis, rivaroxaban prophylaxis had a significantly higher efficacy in comparison with enoxaparin prophylaxis [28–31].

Friedman *et al.* [32] compared patients with BMI more than or equal to 40 kg/m<sup>2</sup> versus below 40 kg/m<sup>2</sup> versus less than 40 kg/m<sup>2</sup> in orthopedic surgery as regards the efficacy of rivaroxaban and found no incidence differences in the rates of DVT, bleeding, or pulmonary embolism [33].

In our study, we compared between both groups as regards the incidence of complications, bleeding grade,

recorded cases of hemoglobin drop during follow-up CBC, and any detected cases of abdominal bleeding or Perigastric hematoma, and any detected cases of DVT in LL venous duplex.

We conducted our study to assess the safety and efficacy of oral anticoagulation after sleeve gastrectomy and consider patient compliance and satisfaction with the oral drug in contrast to subcutaneous injectable drug.

As regards age, no statistically significant difference was found between both study groups. As regards minor bleeding (petechial bleeding grade 1) complications, we found that one (0.3%) case has had petechial patches in the LMWH group in contrast to 40 (13.3%) cases that have had ecchymosis in rivaroxaban group, especially around wounds, which is statistically highly significant.

**Table 4 Comparison between study groups as regards laboratory investigations (hemoglobin drop)**

	Groups [n (%)]		P	Significance
	LMWH	Rivaroxaban		
HGB drop on follow-up CBC				
Negative	298 (99.3)	298 (99.3)	1.0	NS
Positive HGB drop	2 (0.7)	2 (0.7)		
HGB drop on follow-up CBC				
Negative	298 (99.3)	298 (99.3)	1.0	NS
Drop by about 2 g/dl	2 (0.7)	1 (0.3)		
Drop by about 6 g/dl	0	1 (0.3)		

CBC, complete blood count; HGB, hemoglobin; LMWH, low-molecular-weight heparin.

**Table 5 Comparison between study groups as regards follow-up radiological investigations**

	Group [n (%)]		P	Significance
	LMWH	Rivaroxaban		
Follow-up U/S				
Normal	298 (99.3)	299 (99.7)	1.0	NS
Perigastric hematoma	2 (0.7)	1 (0.3)		
LL venous duplex				
Clinically negative	300 (100.0)	300 (100.0)	N/A	N/A

LL, lower limb; LMWH, low-molecular-weight heparin; U/S, ultrasound.

In contrast to that, as regards moderate-to-major bleeding (grade 2) complications, we found that 12 (4%) cases have had perigastric hematoma in the LMWH group in contrast to one (0.3%) case in rivaroxaban group, which is statistically highly significant.

In the LMWH group, 12 cases have had a perigastric hematoma postsleeve gastrectomy discovered in pelviabdominal CT, two of them have had a U/S finding of collection around the stomach (Fig. 1). Pelviabdominal CT with oral contrast was requested to all complaining patients even if routine U/S done after 3 days from the operation was free or no significant laboratory abnormality was found. In total, 10 cases were managed conservatively and two of them necessitate laparoscopic evacuation (large sized), after evacuation, one of them was found to be infected with hematoma and leakage happened after that, which was managed with mega-stent insertion.

Laboratory hemoglobin drop was only positive in two cases of both groups, although 12 cases have had perigastric hematoma in the LMWH group (two was large) with only one case in rivaroxaban group that had hemoglobin drop by about 6 g/dl and severe hematemesis. So sensitivity is very weak to predict bleeding complications, especially if mild.

But actually, no cases in LMWH had a severe bleeding in contrast to one case that had severe hematemesis in rivaroxaban group with hemoglobin drop by about

6 g/dl. It was managed conservatively with blood transfusion with upper endoscopy that showed that there was no definitive offender bleeder to control.

Some systematic reviews and network meta-analysis favor apixaban more than rivaroxaban in different circumstances. Apixaban has been reported to be associated with less gastrointestinal bleeding than rivaroxaban, but actually these studies were conducted on patients with cardiac diseases with long-term use of DOACs [34].

U/S was free for both groups, except in two cases in the LMWH group and one case in rivaroxaban group found perigastric hematoma. Although 12 cases have had perigastric hematoma diagnosed with CT pelviabdominal with oral contrast, only two of them were U/S positive for perigastric hematoma. But throughout the study, no detectable portomesenteric vein occlusion or thrombosis in routine U/S was done 3 days postsleeve gastrectomy even if the patient is not complaining. No clinically suspected LL DVT throughout the study with no need to do LL venous duplex. Rivaroxaban has high plasma protein affinity and extremely bound to it and has a low tissue affinity, so neither increased body weight nor bariatric surgery significantly affect the drug parameters [35]. It was a cause of limitations in our study due to lack of plasma-level testing of the drug, so we excluded one anastomosis gastric bypass patient from our study because of malabsorption portion of that operation.



## Conclusion

Rivaroxaban is a safe and effective alternative to LMWH in prophylaxis of portomesenteric and LL DVT after sleeve gastrectomy with better compliance and more patient satisfaction to the oral alternative.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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