Postoperative enoxaparin vs fondaparinux in prophylaxis against venous thromboembolism in patients undergoing laparoscopic sleeve gastrectomy

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Introduction
Although bariatric surgeries are regarded as safe procedures, yet venous thromboembolism (VTE) remains a challenging problem. Pulmonary embolism presents as the second leading cause of mortality after leakage in bariatric surgery patients. At present, there is no consensus which prophylactic approach, agents, dosing, timing, or duration, is best in the perioperative period for bariatric surgery patients.
Objective
This is a prospective randomized trial aimed at comparing the prophylactic efficacy of enoxaparin currently used with the newer drug fondaparinux in VTE prevention and reducing mortality for patients undergoing laparoscopic sleeve gastrectomy.
Patients and methods
A total of 60 patients undergoing laparoscopic gastrectomy of the sleeve were enrolled in this study. The patients were split into two groups: group A, which included 30 patients who received postoperative enoxaparin at a dosage of 40 mg subcutaneously once daily and group B included 30 patients who received fondaparinux 2.5 mg subcutaneously once daily. The anticoagulation in both groups was continued for 2 weeks.
Results and conclusion
The two groups had similar characteristics with respect to age, procedure time, postoperative hospital stay, and morbidity. Both enoxaparin and fondaparinux tend to be similarly true and successful in reducing the risk of VTE in cases of laparoscopic sleeve gastrectomy.
Disclosure
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Keywords:
deep venous thrombosis, laparoscopic sleeve gastrectomy, venous thromboembolism

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Introduction

Bariatric surgeries are surgical procedures aiming at weight loss for morbidly obese people [1,2]. Although bariatric surgeries are regarded as safe procedures, yet venous thromboembolism (VTE) remains a challenging problem. Pulmonary embolism (PE) presents as the second leading cause of mortality after leakage in bariatric surgery patients being responsible for approximately 40–50% of the deaths. Those patients had multiple risk factors for VTE including morbid obesity itself, older age group, male sex, history of previous deep vein thrombosis (DVT) and PE, and obstructive sleep apnea. [3–5].

VTE prevention is therefore important, and most bariatric surgeons today use a combination of steps, which include graduated compression stocks, intermittent pneumatic compression products, and low-molecular-weight heparin (LMWH) subcutaneously [6]. There is currently no consensus on the prophylactic treatment, agents, dose, pacing, or length that is best for patients with bariatric surgery during the perioperational period [7,8].

Optimal LMWH dosage to prevent VTE in bariatric surgery should be balanced between prevention of DVT or PE and bleeding complications. Many different types of LMWH are present, but enoxaparin is a commonly used agent. Fondaparinux is a newer synthetic drug that specifically inhibits the Xa factor [9–11].

Objective

The aim of the present study was to compare the prophylactic efficacy of the commonly used enoxaparin with the newer agent, fondaparinux, in VTE prevention and reducing mortality for patients undergoing laparoscopic sleeve gastrectomy.

Patients and methods

This prospective randomized trial was conducted in Ain Shams University Hospitals in association with Helwan University Hospital from January 2019 and January 2020. The trial included 60 patients with morbid obesity undergoing laparoscopic sleeve gastrectomy. Patients were randomly divided into two groups using block randomization on the day of surgery in a 1 : 1 ratio. The first group (group A) included 30 patients who received enoxaparin at a dosage of 40 mg subcutaneously once daily. The second group (group B) included 30 patients who received fondaparinux 2.5 mg subcutaneously once daily. The anticoagulation in both groups was continued for 2 weeks postoperatively unless DVT occurred, and patients were turned on therapeutic doses of anticoagulation.

This study was approved by our Department Ethical Committee, and an informed consent about this study, details of the procedure, and postoperative follow-up protocol was obtained from all patients.

Patient population

All male and female patients who underwent laparoscopic sleeve gastrectomy for morbid obesity were included in this study. Patients were eligible for the study if they were 18 years or older with a BMI of 35 kg/m^2 or greater and moderate-risk patients for DVT (VTE risk assessment score 3–4 according to Caprini scoring system).

Exclusion criteria were patients with contraindications to LMWH or selective antithrombin III agonists, history of previous VTE (DVT or PE), documented congenital/acquired coagulation disorders, history of treatment for cancer, pregnancy, thrombocytopenia, history of vein stripping or ligation, active or recent clinically significant bleeding, active peptic ulcer, known colonic angiodysplasia, severe uncontrolled hypertension, and patients refused to participate in the trial.

Preoperative assessment included full history, general examination, and local abdominal examination to detect any abdominal wall hernias. Calculation of BMI and risk assessment for VTE were done. Patients were recommended to stop smoking for at least 6 months before surgery. All patients were invited to a multidisciplinary team meeting consisting of bariatric surgeon, clinical nutritionist, psychiatrist, and anesthetist.

Routine investigations were requested for all patients. Special investigations for all patients included upper gastrointestinal endoscopy and thyroid function tests. Echocardiography was done for patients more than 50 years old or BMI greater than or equal to 50 kg/m^2 or if requested by the anesthetist.

Elastic stockings were placed preoperatively before induction of anesthesia and continued for 6 hours postoperatively, and the patients were strongly encouraged for early ambulation.

Surgical technique

A single preoperative dose of parenteral third generation cephalosporin was administered for anesthesia induction. General anesthesia has been regularly administered.

The patient was positioned in a steep reverse Trendelenburg position in split leg (French) position with both arms extended and graduated compression stockings are applied to the lower limbs. Pneumoperitoneum was established using Veress needle inserted in supraumbilical region.

Standard five-port technique was used in all cases. After liver retraction, the pylorus was identified and then the greater curvature was dissected free from the greater omentum via laparoscopic ultrasonic scalpel starting 5 cm from the pylorus up to the Angle of His. Guided by an esophageal bougie, a laparoscopic linear cutting stapler was introduced to serially staple and transect the stomach and the transected stomach removed from the abdominal cavity through the left upper quadrant port incision. Using methylene blue infused into the bougie, the staple was tested for leakage and complete hemostasis was verified. We used 18-F Redivac drain along the staple line.

Postoperative follow-up

Early ambulation of patients was encouraged as early as possible. Prophylactic anticoagulation started at the night of the surgery (12 h after the operation) and for 2 weeks postoperative. To be noted, we chose enoxaparin dose according to the general agreement of most previous clinical trials, as there were no standard guidelines regarding optimal dosage.

Regarding postoperative diet, patients had a clear fluid diet for the first week, then Puree diet for the next two weeks, and then soft diet for 2 weeks.

Routine gastrograffin meal test was performed in all patients in the first postoperative day before allowing oral intake. All patients were discharged in the second postoperative day if they can tolerate oral liquid diet.

VTE detection protocol

In the present study, we used three methods for DVT detection, including first, complete history and physical examination for symptoms and signs of DVT or PE such as lower limb edema, pain, tender calf muscles, tenderness on dorsiflexion of the foot (Homans sign), dyspnea, chest pain, or blood-stained cough; second, bilateral Duplex study of the lower limb venous system (femoral, deep femoral, popliteal, posterior and anterior tibial, fibular and calf muscular veins) for vessel noncompressibility, hypoechogenic thrombi, the absence of spontaneous and phasic flow during breathing and the non-increase in flow during compression maneuver; and third, D-dimer level assay owing to its high sensitivity (≥97%), ease, and cheap testing, and we used it to rule out DVT.

Our plan was to collect those data at day 1, 7, 14, and 30 days postoperatively. Moreover, postoperative bleeding, complications, and death were recorded.

Statistical analysis

Statistical analysis was performed using Windows version 20.0 of IBM SPSS Statistics [SPSS Statistics is a software package used for interactive, or batched, statistical analysis. Long produced by SPSS Inc., it was acquired by IBM in 2009. Current versions (post 2015) have the brand name: IBM SPSS Statistics]. The results were compared with the Student t test for continuous variables and the χ^2 with the Yates correction or Fisher exact tests for categorical variables. A P value less than 0.05 was considered to be statistically significant.

Results

Demographics and patients' related data

In terms of age, sex, BMI, preoperative comorbidities, and gastroesophageal reflux disease, there was no substantial difference (Table 1).

Operative data

The operating data are shown in Table 2. There was no significant difference between the two classes in terms of operational time, blood loss, and complications of the interoperation. The mean operating time in group A was 123.07±25.36 min, and in group B was 126.47 ±20.03 min. Blood loss in group A was measured at 38.33±9.86 ml, and in group B, at 41.67±8.02 ml. There were no instances of open process conversion.

Postoperative data

Postoperative data are summarized in Table 3. The postoperative period during hospital stay had no major adverse events, apart from three patients (one in group A and two in group B) experiencing increased drain sanguineous output on the postoperative day 1,

Table 1 Demographics and patients' related data

Variables	Group A [*n* (%)]	Group B [*n* (%)]	*P* value
Number of patients	30	30	
Age (mean±SD) (years)	38.33±6.13	38.07±5.63	0.86 (NS)
Sex (male : female)	5 : 25	10 : 20	0.23 (NS)
BMI (mean kg/m2±SD)	41.63±4.52	42.37±4.82	0.55 (NS)
Comorbidities			
Hypertension	25 (83.3)	27 (90)	0.71 (NS)
DM (type 2)	11 (36.6)	8 (26.6)	0.58 (NS)
Obstructive sleep apnea	1 (3.3)	0	1 (NS)
GERD	4 (13.3)	6 (20)	0.73 (NS)
VTE risk assessment score			
Score 3	2	5	0.4238 (NS)
Score 4	28	25	

DM, diabetes mellitus; GERD, gastroesophageal reflux disease; VTE, venous thromboembolism.

Table 2 Operative data

	Group A	Group B	*P* value
Operative time (min)	123.07±25.36	126.47±20.03	0.57 (NS)
Blood loss (ml)	38.33±9.86	41.67±8.02	0.16 (NS)

which was managed conservatively, and the patients did not receive any blood transfusion. All patients in both groups were discharged on the second postoperative day. There was no dysphagia and no mortality. No patient required reoperation. Eight patients were readmitted due to abdominal pain, and ultrasound detected intra-abdominal collection. Pelviabdominal computed tomography with contrast was done, and two patients were diagnosed to have leakage. Endoscopic stenting was done for 6 weeks and then after removal of the stent, both patients had their leak completely healed. The other six patients were treated conservatively, and follow-up computed tomography scan showed complete resolution of the abdominal collection.

Postoperative VTE

Regarding the occurrence of DVT, there was no statistical disparity between the two groups as shown in Table 4. Complete history and physical examination of all patients in both groups at the scheduled follow-up visits revealed no symptomatic postoperative DVT or PE.

Bilateral color Duplex study of the lower limb venous system revealed two cases of VTE complications in the form of one case of asymptomatic distal (calf muscular veins) DVT in group A (3.3%) and one case of asymptomatic proximal (popliteal vein) DVT in group B (3.3%). This was discovered at the first postoperative outpatient follow-up visit (day 7).

Confirmation of the aforementioned results by D-dimer level assay showed two cases of elevated D-dimer level (one case in each group).

Table 3 Postoperative data

	Group A [*n* (%)]	Group B [*n* (%)]	*P* value
Minor drain bleeding	1 (3.3)	2 (6.6)	1 (NS)
leakage	1 (3.3)	1 (3.3)	1 (NS)
GERD	4 (13.3)	6 (20)	0.73 (NS)
ICU admission	6 (20)	3 (10)	0.47 (NS)

GERD, gastroesophageal reflux disease.

Table 4 Results of VTE detection work-up

	Group A [*n* (%)]	Group B [*n* (%)]	*P* value
Positive duplex study (*N*)	1 (3.3)	1 (3.3)	1 (NS)
Elevated D-dimer level (*N*)	1 (3.3)	2 (6.6)	1 (NS)

VTE, venous thromboembolism.

Both patients were males, age above 50 (51 and 55) years, BMI above 50 (50.2 and 51.6, respectively), VTE risk assessment score 4, and both had DM.

Discussion

Bariatric surgical procedures had proved its effectiveness now as a valid method of obesity treatment, but the American College of Chest Physicians' Consensus [3–5] had defined bariatric surgery as high risk for development of VTE, with estimated risk of developing distal DVT up to 80% and up to 20% proximally, with up to 5.0% incidence of fatal PE if no appropriate prophylactic dosage of anticoagulation was given.

Single-agent thromboprophylaxis in combination with other mechanical prophylaxis like early ambulation and shorter hospital stay are very important factors to decrease the overall VTE rates in bariatric surgery [12].

LMWH is one of the most often used regimen for bariatric surgery patients as concluded by a meta-analysis conducted by Becattini *et al.* [8], of which enoxaparin and fondaparinux are the most used agents.

The aim of the present study is to compare the efficiency of enoxaparin and fondaparinux in the prevention of adverse VTE events after LSG.

Regarding the dose, we chose enoxaparin 40 mg once daily starting postoperative only, whereas in other studies, like The EFFORT trial [10] and Scholten *et al.* [8], they used enoxaparin 40 mg twice daily, but according to a study published by Javanainen *et al.* [11], there was no statistical differences between both regimens regarding VTE events.

For fondaparinux, we chose 2.5-mg dose once daily as recommended by many studies [13] than the 5-mg dose which was revised in some clinical trials [10].

LSG is the most commonly performed bariatric operation in our country, so we specifically evaluated that regimen in this procedure to eliminate any counterfeit with other bariatric operation regarding longer intraoperative time, more perioperative chances of bleeding, and possible longer hospital stay.

In the present study, we randomly divided the patients into two groups (A and B). Group A received enoxaparin 40 mg once daily, whereas group B received fondaparinux 2.5 mg once daily. Patients in both groups continued the use of anticoagulation for 2

weeks postoperatively. There was no statistically significant difference between both study groups regarding the age, sex, BMI, and preoperative co-morbid conditions.

Some studies recommended a preoperative dose of thromboprophylaxis, but as recommended by Altieri *et al.* [14], we followed postoperative prophylaxis only to decrease VTE incidents, while minimizing bleeding complication.

In relation to the adverse events especially bleeding, our study had three cases of minor bleeding in the form of increased drain output (one case in group A and two cases in group B), that was 5% of all cases, which is relative to other studies such as Steele *et al.* [10] (4%) and Imberti *et al.* [15] (5.6%).

In the present study, we used conventional, cost-effective approaches to detect DVT in the form of clinical (history and examination), radiological (color Duplex study), and biochemical (D-Dimer assay) tests.

Other methods for VTE detection after bariatric surgery like the antifactor Xa levels and magnetic resonance venography were used in the EFFORT trial [10] and the BAFLUX study [15].

In the present study, no cases of symptomatic DVT or PE were reported, in agreement with other studies [10,11,15]. Two cases of DVT (one in each group) were reported with bilateral color Duplex study and D-dimer level assay confirmation, which turned out VTE incidence in this study to be 3.3%. Other trials ranged VTE from 0.3 to 3.8% despite these interventions [10,16,17].

Owing to the small number of confirmed DVT cases in our study, we could not relate our results to possible risk factors that could be the predisposing factors of developing VTE complications after laparoscopic sleeve gastrectomy, but both positive cases were diabetic males, age more than 50 years, and higher BMI (above 50). Those factors might be associated with higher DVT incidence.

Patients diagnosed with DVT received therapeutic doses of parenteral and oral anticoagulation for 3 days followed by oral anticoagulation for 6 months.

To be noted that in this study, Caprini scoring system was used for patients' VTE risk assessments [18].

Limitations

This research is not without restrictions. The number of patients mostly is small.

Further randomized controlled trials with a larger sample size are needed for definitive validation of daily clinical practice for VTE prophylaxis in bariatric surgery.

Conclusion

Both enoxaparin and fondaparinux appear to be equally valid and effective regimen at reducing the risk of DVT and PE in cases of laparoscopic sleeve gastrectomy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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