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Fondaparinux to Prevent Venous Thromboembolism after Bariatric Surgery: An Observational Clinical Trial

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Abstract

Background: Bariatric surgery is associated with a higher risk of thromboembolism complications and requires longer thromboprophylaxis. After hospital discharge, we could use Fondaparinux. This study aimed to assess the effectiveness of Fondaparinux use for postoperative thromboprophylaxis after bariatric surgery.

Methods: This prospectively collected data study of consecutive patients undergoing bariatric surgery given Enoxaparin for prophylaxis (40 mg single dose immediately after surgery) followed by Fondaparinux after hospital discharge (2.5 mg to 5 mg for 10 days to 15 days). The outcomes measures were evaluated by questioning, computed tomography, postoperative thromboembolic, and bleeding. The follow-up was of 12 months.

Results: One hundred fifty-four patients were enrolled. Eighty-five patients were discharged on the day of surgery and 86 patients on the following day. Before discharge (during Enoxaparin thromboprophylaxis), one patient was identified with asymptomatic pulmonary embolism, one with a major bleeding event, and seven with minor bleeds. One hundred thirty-eight patients (89.6%) were evaluable at 12 months. After discharge, there is no thromboembolic or bleeding events. None of the patients died during the follow-up.

Conclusion: Fondaparinux appears safe when used for postoperative thromboprophylaxis following bariatric surgery.

Keywords: Fondaparinux; Enoxaparin; Venous thromboembolism; Thromboprophylaxis; Bariatric surgery; Laparoscopy; Bleeding

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Introduction

Venous Thromboembolism prophylaxis (VTE) with heparin derivatives has entered routine clinical practice after obesity surgery. It depends on the procedure and the patient's risk profile [1]. Especially bariatric surgery carries a particularly higher risk [2,3]. It may involve reduced mobility and pre-existing inflammatory prothrombotic status [2]. Pulmonary embolism presents 30% on the grounds of mortality after bariatric surgery [4]. VTE prevention for obese patients is an important medical issue; few interventional studies aimed to define the optimal thromboprophylaxis regimen, and there is a lack of strong recommendations [5]. The 2018 European and French guidelines recommended prophylaxis with a higher dose of Low Molecular Weight Heparins (LMWH), associated with mechanical prophylaxis by an intermittent pneumatic compression during 10 to 15 days after hospital discharge [6,7]. LWMH has several advantages over Unfractionated Heparin (UFH), essentially the administration route, absence of coagulation status motoring, and lower risk of thrombocytopenia. In 2017, a French national survey reported the use of LWMHs, principally Enoxaparin, in more than 90% of cases after bariatric surgery [5].

Fondaparinux is a synthetic pentasaccharide heparin analogue. It presented a specific anti-Xa anticoagulant mechanism. It ensures a lower risk of thrombocytopenia than conventional LMWHs, with a pharmacokinetic profile that enables once-daily dosing across the dose range [7]. After bariatric surgery, a randomized, double-blind clinical trial (EFFORT) has compared Fondaparinux

5 mg, once daily, to Enoxaparin 40 mg, twice daily, in terms of VTE thromboprophylaxis [8]. In the Fondaparinux group, A higher number of patients achieved target anti-factor Xa activity than the Enoxaparin group, with a similarly low incidence of VTE events (2% - all asymptomatic deep vein thrombosis) and bleeding complications (≤ 5% - all minor). Despite the encouraging findings of the EFFORT trial, currently, limited data are available concerning the effectiveness and safety of Fondaparinux use after bariatric surgery. This observational trial aimed to assess the effectiveness of Fondaparinux after Laparoscopic Sleeve Gastrectomy (LSG) to prevent VTE.

Methods

We conducted a prospectively collected data study, including consecutive obese patients undergoing LSG in France's reference obesity treatment center. The study period was between January 1st, 2018 and December 31st, 2018.

Patients

Obese patients undergoing LSG during the inclusion period were evaluated. The indication for LSG complied with French guidelines [9]. All patients had a body mass index (BMI) >40 kg/m² or ≥ 35 kg/m² with at least one associated comorbidity. They underwent a comprehensive evaluation before surgery by a multidisciplinary team: nutritionist, gastroenterologist, psychiatrist, dietician, anesthetist and bariatric surgeon.

Surgical procedure

Sleeve gastrectomy was performed using a single-port device or a multiport and 10-mm flexible tip laparoscope (LTF-VH or EndoEYE LS, Olympus Medical) [10].

Treatments

Enoxaparin (40 mg) was given 6-hour after surgery. For patients remaining in hospital overnight, the second dose of Enoxaparin 40 mg was given the next morning, before discharge. In all cases, the patient started the Fondaparinux treatment at home, the first injection at 6 h to 12 h after Enoxaparin. The Fondaparinux treatment regime was 2.5 mg/day (in patients with a BMI<50 kg/m² and weighing <150 kg) or 5 mg/day (in patients with a BMI ≥ 50 kg/m², weighing ≥ 150 kg or with a history of VTE) for ten days. Fondaparinux was administered at home by a nurse. Regarding the short duration and the early patient's mobilization, mechanical compression was not considered.

Evaluations

Computed Tomography (CT) with intravenous and oral contrast agents was performed systematically on the first 48 h after surgery to identify postoperative complications. After hospital discharge, patients were followed daily by a qualified nurse throughout the Fondaparinux treatment. We monitored vital signs and any adverse effects at the injection site; symptoms of VTE or bleeding events were documented. Standard laboratory tests (full blood count and serum biochemistry) were performed routinely on days two and eight. After one month of follow-up, patients returned for the out-point clinic, and the surgeon checked any symptoms of side effects like VTE or bleeding.

Patients were examined at three, six, and twelve months after surgery. They were asked about any VTE or bleeding events symptoms. In addition, we performed a comprehensive evaluation and a CT scan with an oral opacification to identify any late complications at 12 months after surgery.

Data collection

Data were prospectively collected and analyzed. Demographic information included age, gender, height, and weight. Comorbidities of interest (hypertension, diabetes, dyslipidemia and sleep apnea) were identified. Any medical history of VTE was documented, together with any relevant morbidity.

Outcomes

We evaluated the symptomatic VTE events reported by the patients during the 12-month of follow-up, VTE events identified in the CT-scan, and bleeding episodes objectified by the patients or in the CT-scan.

Statistical analysis

Data presentation is purely qualitative. Missing data were not replaced.

Ethics

The study was conducted according to relevant international and French legislation and followed Good Clinical Practice. This study was approved by the French Society of Obesity Surgery and Metabolic Diseases (SOFFCO.MM) and by the Institutional Independent Ethics Committee of the Institute Mutualiste Montsouris (Authorization No. CEPAR: 2020-04, cepar@imm.fr). Before surgery, each eligible patient was provided with a study information leaflet and provided written consent.

Results

Participants

We included 154 patients. The demographic characteristics are presented in Table 1. The majority of patients were women (59.7%), the mean age was 40 years, and the median BMI was 43.6 kg/m². The most frequent comorbidity was sleep apnea (61%). We noted a past medical history of venous thromboembolism in four patients (2.6%), and there was no past surgical history in 66 patients (42.9%). One patient was lost of follow-up.

Surgery

Laparoscopic surgery was performed using a single-port in 80 patients; two patients with a history of gastric surgery required an additional trocar, and 74 patients operated using multiple trocars. The median operative time was 46 min [IQR 29 min to 160 min]. There was no conversion to laparotomy with a median hospital of one day [IQR: 0 to 8 days]. Fifty-eight patients were discharged on the first day after surgery. Six to eight hours after surgical procedure, 77 patients were discharged on the day following surgery, and the remaining nine patients were between the fifth and eighth days (Table 2).

Thromboprophylaxis

Fondaparinux thromboprophylaxis was at the dose of 2.5 mg in 119 patients and 5 mg in 34 patients. An asymptomatic pulmonary embolism was identified before discharge in one patient. Then he received Fondaparinux at the dose of 7.5 mg for six months (Table 2).

VTE events

We did not identify any symptomatic VTE during the 12-month follow-up. An asymptomatic pulmonary embolism was diagnosed before patient discharge during thromboprophylaxis with Enoxaparin in a single patient with no previous history of VTE. The diagnosis was made using a CT scan behind patient complaints of chest pain on the first day of hospitalization. Vital signs were

Table 1: Demographic data of included patients.

Demographic data	N=154
Age (years; mean ± SD)	40.1 ± 12.3
Gender	
Men (n %)	62 (40.3%)
Women (n %)	92 (59.7%)
Weight (kg; median [IQR])	118 [84-222]
Body mass index (kg/m²; median [IQR])	43.6 [33.8-74.4]
<40 kg/m²	39 (25.3%)
40-50 kg/m²	87 (56.5%
>50 kg/m²	28 (18.1%)
Comorbidities (n, %)	
Diabetes	25 (16.2%)
Hypertension	61 (39.6%)
Dyslipidemia	42 (27.2%)
Sleep apnea	94 (61.0%)
Treated	*33(21.4%)*
History of venous thromboembolism	4 (2.6%)
Past surgical history (n, %)	
Any surgery	66 (42.9%)
Upper gastrointestinal surgery	30 (19.5%)

IQR: Interquartile Range; SD: Standard Deviation

Table 2: Postoperative outcomes.

Outcome	Results
Surgical approach	
Single-port	80
Multy-port	74
Operative time: min [IQR]	46 [29-160]
Hospital stay: day [IQR]	1 [0-8]
Morbidity	
Fistula	1
Pulmonary embolism	1
Symptomatic VTE	0
Asymptomatic VTE	1
Hematoma	7
Bleeding	1
% EWL at 12-month	69.6 ± 24.5%
Mortality	0

unchanged, and symptoms disappeared on the same day. The patient continued treatment with Enoxaparin in hospital until day 5 to achieve adequate factor Xa activity. The patient was discharged home, and Fondaparinux switched the treatment on the same day. No further factor Xa activity monitoring was performed. The patient has been treated with Fondaparinux 7.5 mg for six months, and the event resolved without clinical manifestations. A CT pulmonary angiogram performed at three months and a second at twelve months were normal. No cases of Deep Vein Thrombosis (DVT) or portal thrombosis were detected. No other VTE events were reported over the follow-up period. There was no indication of VTE on the CT scans performed at twelve months (Table 2).

Bleeding events

Bleeding episodes or hematomas were reported in eight patients. All events were reported during the hospital stay when patients were still receiving Enoxaparin. These were considered acute complications of surgery. Minor bleeds or hematomas on the gastric staple line without clinical manifestations were reported in seven patients treated conservatively. Enoxaparin was stopped after three days, and treatment by Fondaparinux started at home at the standard dose on Day 4 after surgery. An additional patient required a blood transfusion (two packed red blood cells) that failed to control the bleeding. A second laparoscopy was thus needed (gastric staple line) on Day 2 after surgery, which resolved the bleeding. The patient was discharged on day 8. We did not identify further bleeding episodes during the follow-up period (Table 2).

Surgical outcome

There was no mortality. As a concern the morbidity, one patient presented fistula. It was identified on a postoperative CT scan performed on the first day after surgery. An endoscopic stent was adopted. Four patients presented an incisional hernia. Three out of these four patients were operated on using multiple ports. Other benign abdominal wall complications, such as delayed scar formation or keloids, were observed in a further ten patients.

After12 months of follow-up, the mean excess weight loss was 69.6% ± 24.5%. The median weight decreased from 121 [IQR: 84–222] kg to 86 [46–182] kg, and median BMI decreased from 42.8 [34.9–84.6] kg/m² to 31.2 [20.7–91.8] kg/m². Significant reductions of associated comorbidities were observed (Figure 1).

Discussion

This prospective observational cohort study, in a naturalistic treatment setting, evaluated patients undergoing LSG receiving postoperative thromboprophylaxis with Fondaparinux. It demonstrated a low rate of VTE outcome (<1%), with a single case of asymptomatic perioperative PE during thromboprophylaxis with Enoxaparin.

Bariatric surgery is considered at high risk for VTE due to the nature of the procedure itself and patient-related comorbidities [3,5]. In an American hospital discharge database, the prevalence of postoperative VTE in a population of more than 500,000 patients undergoing bariatric surgery between 2007 and 2009 was 0.9% for PE, 1.3% for DVT and 2.2% for all VTE events [11]. In addition, a meta-analysis of VTE-related outcomes following laparoscopic bariatric surgery and thromboprophylaxis with UFH or LMWH reported an incidence rate of 0.6% for symptomatic DVT and 0.5% for PE [12]. In another meta-analysis of 25 randomized clinical trials comparing Fondaparinux to placebo or LMWH, the Incidence of total VTE was 2.2% in studies *vs.* placebo and 6.0% in studies versus LMWH [13]. The present findings can also be compared to those of studies of UFH or LMWH in bariatric surgery. An earlier meta-analysis reported an odds ratio for all VTE of 0.24 for Fondaparinux compared to placebo and 0.55 for Fondaparinux compared to LMWH [14]. A meta-analysis involving twelve studies that compared the efficacy and safety of Fondaparinux and LMWH for perioperative surgical thromboprophylaxis determined an odds ratio of all DVT events of 0.49 for patients treated with Fondaparinux compared to those receiving LMWH and an odds ratio for major bleeding of 1.48 [12]. They concluded that Fondaparinux presented a higher net clinical benefit than LMWH when both VTE and bleeding events were

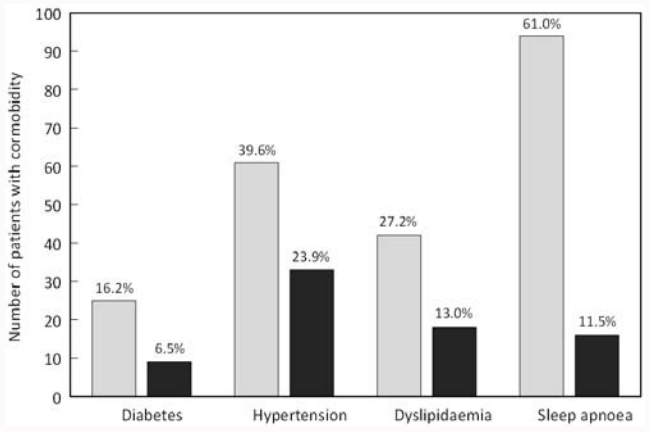

Figure 1: Patient with comorbidities at baseline and twelve months after surgery.
Pale grey columns: Patients with comorbidity at baseline; Dark grey columns: Patients with comorbidity at twelve months are following bariatric surgery. Data are presented as the absolute number of patients with the percentage indicated above each column.

considered.

In particular, the EFFORT study compared Fondaparinux to Enoxaparin after laparoscopic bariatric surgery [8]. To our knowledge, this is the only randomized interventional trial that has evaluated Fondaparinux in the area of bariatric surgery. The primary outcome was factor Xa activity and the Incidence of DVT, including asymptomatic DVT, assessed by systematic magnetic resonance venography. The Incidence of DVT was similar in Fondaparinux and Enoxaparin groups (2%). The present study has several differences with the EFFORT trial, notably using a low-risk surgical procedure, LSG, in all patients and day-hospitalization ensuring rapid mobilization, which would be expected to be associated with a lower rate of VTE. On the other hand, this study enrolled patients operated in the reference center, including severely obese patients and patients with chronic obstructive respiratory disease and smokers, who had a higher VTE risk and were not retained in the EFFORT trial.

In this study, a single dose of Fondaparinux 2.5 mg per day was administered in 77% of patients; the remainder received the double dose of 5 mg qd. The standard dose appeared effective, although Factor Xa activity was not determined. This would be useful to assess in a dedicated study. The possibility of using the standard dose of 2.5 mg of Fondaparinux was reassuring from a safety perspective. In particular, this may limit the bleeding risk, which in other perioperative settings is higher for Fondaparinux than for Enoxaparin [12].

Fondaparinux may present specific advantages compared to LMWH in patients after bariatric surgery. A single daily dose, fewer injections were needed than LWMH, with better patient convenience during the postoperative period. Secondly, as demonstrated in the EFFORT study, factor Xa rate activity was greater in the Fondaparinux 5 mg qd group than Enoxaparin 40 mg bid group [8]. This finding is relevant because it has known that the optimal thromboprophylaxis dose of Enoxaparin after bariatric surgery based on BMI is difficult to achieve [15,16]. In addition, Fondaparinux carries a low risk of thrombocytopenia, obviating the need for platelet monitoring for patients with difficult venous access and reducing healthcare costs.

The increased risk of VTE after bariatric surgery persisted for several months [17]. In the present study, the duration of Fondaparinux administration was suggested arbitrarily at ten to fifteen days. However, this duration may not be optimal, and further studies would be required to determine the most appropriate treatment duration.

This study's advantages include the relatively large sample size, the wide-ranging eligibility criteria (all patients undergoing bariatric surgery), the low proportion of patients lost to follow-up at twelve months (1%), and the naturalistic treatment setting. These aspects should permit broad generalization of the findings. Limitations include the absence of a comparator group and the absence of systematic detection of VTE by Doppler ultrasonography or pulmonary angiography at each follow-up consultation. However, these limitations were intrinsic to the naturalistic treatment setting.

In conclusion, this study contributed to the very sparse literature on Fondaparinux in bariatric surgery. It confirmed the available data in the literature. In particular, combining a minimally invasive surgical technique with postoperative thromboprophylaxis with Fondaparinux ensured a low VTE rate without bleeding risk.

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