Prophylaxis with rivaroxaban after laparoscopic sleeve gastrectomy could reduce the frequency of portomesenteric venous thrombosis

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ABSTRACT

INTRODUCTION Portal and mesenteric venous thrombosis is a rare but potentially serious complication after laparoscopic sleeve gastrectomy. There are no consistent studies that prove the safety and effectiveness of oral anticoagulant thromboprophylaxis with rivaroxaban after laparoscopic sleeve gastrectomy. The objective was to evaluate the effect of rivaroxaban on the frequency of portal and mesenteric venous thrombosis and its safety profile after laparoscopic sleeve gastrectomy.

MATERIALS AND METHODS This retrospective analysis of prospectively collected data includes all laparoscopic sleeve gastrectomies performed by a single surgeon at Pontificia Universidad Católica de Chile Hospital between January 2009 and June 2019. All patients received low molecular weight heparin thromboprophylaxis during the whole hospital stay. Between July 2012 and June 2019, patients received additional post-discharge thromboprophylaxis with rivaroxaban. Patient demographics, impaired renal, post-surgical portal and mesenteric venous thrombosis, and bleeding episodes were registered.

RESULTS A total of 516 patients were identified; 95 patients were excluded. Results for 421 patients were analysed: 198 received only intrahospital thromboprophylaxis (group 1) and 223 received additional post-discharge thromboprophylaxis with rivaroxaban (group 2). There was no statistically significant difference between the two groups concerning age, sex and body mass index. In group 1, four cases of portal and mesenteric venous thrombosis were registered and no cases were reported in group 2 ($p < 0.05$). All cases occurred before 30 days after surgery. No bleeding episodes and no adverse reactions were detected in group 2.

CONCLUSIONS Thromboprophylaxis during the whole hospital stay (two to three days), followed by rivaroxaban 10mg once daily for 10 days after discharge (completing in total 13–14 days of prophylaxis), could reduce cases of post-surgical portal and mesenteric venous thrombosis without an increase in bleeding complications.

KEYWORDS

Bariatric surgery – Laparoscopic sleeve gastrectomy – Venous thrombosis – Portal vein – Portal and mesenteric venous thrombosis

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Introduction

Portal and mesenteric venous thrombosis (PMVT) has been described as a surgical complication after laparoscopic sleeve gastrectomy. PMVT is a rare (0.1–1.8%) but a potentially serious complication. It can lead to intestinal ischaemia, perforation and secondary peritonitis, and may be associated with high mortality rates.^{1–4} Late diagnosis and treatment lead to thrombus organisation with the consequent portal cavernoma and portal hypertension complications including variceal bleeding.^{5–8}

Direct oral anticoagulants, oral direct thrombin inhibitors (dabigatran) and oral factor Xa inhibitor (rivaroxaban, apixaban and edoxaban) have developed as effective and safe

alternatives to classic anticoagulation drugs. They have proven to be effective in orthopaedic surgery, for stroke prevention and in the treatment of venous thromboembolism in selected patients.^{9–17} There are studies comparing the use of direct oral anticoagulants with low molecular weight heparin (LMWH) for the prevention of venous thromboembolism in orthopaedic surgery, in which its use is more effective for prevention of venous thromboembolism without increasing major bleeding risk.^{11–15} Data from meta-analyses and randomised trials of patients with venous thromboembolism report similar efficacy and reduced rates of bleeding when direct oral anticoagulants are compared with vitamin K antagonist.^{18–25}

Several studies have described the pharmacological safety and anticoagulation efficacy of rivaroxaban in sleeve gastrectomy but, to our knowledge, there are no studies reporting the clinical safety and results of the use of rivaroxaban for PMVT prophylaxis after laparoscopic sleeve gastrectomy.^{26–28} This study evaluates the effect of rivaroxaban on the frequency of PMVT and its safety profile in patients who underwent laparoscopic sleeve gastrectomy.

Materials and methods

Patients

This retrospective analysis of prospectively collected data, including all consecutive patients who underwent laparoscopic sleeve gastrectomy by a single surgeon, was performed at Pontificia Universidad Católica de Chile Hospital, Santiago, Chile, between January 2009 and June 2019. This hospital is a tertiary university-affiliated medical centre. Between January 2009 and April 2011, patients received only intrahospital thromboprophylaxis (enoxaparin). In May 2012, because of the number of PMVT events that were occurring in our group,⁵ an additional anticoagulant thromboprophylaxis protocol was initiated at discharge. Between May 2012 and June 2012 patients received additional post-discharge thromboprophylaxis with LMWH. However, because of the difficulty that patients had in self-administering the treatment, between July 2012 and June 2019 all patients received post-discharge thromboprophylaxis with rivaroxaban. Preoperative use of anticoagulation therapy and impaired renal function clearance (creatinine clearance <50ml/minute) were exclusion criteria.²⁹ The university ethical committee approved the study and informed consent was obtained in writing from all participants before they underwent laparoscopic sleeve gastrectomy.

Surgical technique

Every patient is requested to achieve a 5–10% weight loss before surgery. The patient is placed in a supine position with pneumatic mechanical compression of the legs during the whole surgery. The operating surgeon is located on the right side of the patient and the assistant on his left. Pneumoperitoneum is done in a close manner with a direct view port. Five laparoscopic ports are used, with the camera going in through a supraumbilical incision. The greater curvature of the stomach is dissected with an Ethicon Endosurgery Harmonic[®] or a Tyco Healthcare Ligasure[®] from 4–5cm proximal to the pylorus to preserve the gastric antrum partially. For guiding the gastrectomy, a 50-French tube is placed along the lesser curvature. An Ethicon Endosurgery Echelon or Tyco Healthcare EndoGIA stapler is used for the gastric section directed to the angle of his. The stapler line is reinforced with a 3–0 absorbable running suture.

Postoperative care

Patients keep intermittent pneumatic compression during the first 24 hours and begin with LMWH thromboprophylaxis

(enoxaparin 40mg once daily) the same day of operation and during the whole hospital stay. A compression stocking is used after discontinuation of intermittent pneumatic compression. In our pain management, we use acetaminophen (1000mg three times daily) and parecoxib (40mg twice daily) for 48 hours. At postoperative day 1, the patient has a walking routine and begins feeding with a liquid diet. According to clinical progress, the patient is discharged at postoperative day 2 or early on day 3. All patients use omeprazole 20mg twice daily for four months. Since May 2012, patients were prescribed with rivaroxaban 10mg once daily for 10 days after discharge, completing 13–14 days of thromboprophylaxis.

Data analysis and follow-up

Patient demographics, body mass index, impaired renal function (creatinine clearance <50ml/minute by Cockcroft–Gault formula with the use of actual body weight), ambulatory rivaroxaban thromboprophylaxis, post-surgical PMVT or venous thromboembolism, any minor or major bleeding episode according to the International Society on Thrombosis and Haemostasis and characteristic of the patients who experienced PMVT were registered.⁵⁰ Diagnosis of PMVT was confirmed with contrast-enhanced computed tomography (CT) for every patient who presented to the emergency department with abdominal pain in the postoperative period.

The analysis was divided into two groups. Patients who used conventional thromboprophylaxis (only intrahospital thromboprophylaxis) and the second group with additional post-discharge thromboprophylaxis with rivaroxaban.

All patients were followed-up 10 days after the surgery and again the first month after surgery. They were then seen every three months during the first year and every four months during the second year. Any presentation to the emergency department was included in our registry.

Statistical analysis

Categorical data were compared by Fisher's exact test or chi-square test. Continuous variables were examined with the Wilcoxon rank-sum test. Statistical analysis was performed using SPSS version 20.0. Statistical significance was defined as *p*-value less than 0.05.

Results

From January 2008 and June 2019, 516 patients who underwent a laparoscopic sleeve gastrectomy by a single surgeon were identified. There were no patients with creatinine clearance less than 50ml/minute or preoperative use of anticoagulation therapy; 95 patients were excluded from the comparative analysis because they received outpatient thromboprophylaxis with LMWH. No bleeding or venous thromboembolism events were detected in the exclude group during the inpatient stay or the following discharge. The characteristics of the 421 patients analysed are presented in Table 1; 198 patients received only intrahospital thromboprophylaxis (group 1) and 223

received additional post-discharge thromboprophylaxis with rivaroxaban (group 2). There was no statistically significant difference between the two groups concerning age, sex and body mass index.

In group 1, four cases of PMVT were registered and no cases were reported in group 2 ($p < 0.05$). All cases of PMVT occurred before 30 days after surgery. No other venous thromboembolisms or bleeding episodes occurred in these groups (during the inpatient stay or following discharge).

All patients with PMVT arrived at theatre with abdominal pain and were diagnosed with contrast-enhanced CT (Table 1). Follow-up was 100%, 95.7% and 92.6% at 3, 12 and 24 months, respectively.

The demographics of patients with PMVT are detailed in Table 2; 25% of patients having a PMVT event had a subsequently identified hypercoagulable disorder. No other

patient in this series had a hypercoagulable disorder that was known in advance of the surgery.

Discussion

PMVT is defined as thrombosis of the portal vein and/or its branches (superior mesenteric vein and splenic vein).¹ PMVT is a rare but a potentially serious complication with a reported incidence that varies approximately from 0.1% to 1.8%.^{1,3,5-8,31-38} Diagnosis is difficult due to the non-specificity of its symptoms and the condition can lead to intestinal perforation associated with high mortality rates (11–45%).^{1-5,36,39} The main treatment is anticoagulant therapy, but surgery is sometimes necessary where there is, for example, bowel ischaemic necrosis.^{1,59} In our institution, all patients with abdominal pain after bariatric surgery undertake a contrast-enhanced CT scan to exclude surgery-related complications.

Risk factors for PMVT include metabolic syndrome, tobacco smoking, coagulopathy disorders, oral contraceptive usage, an increase of intra-abdominal pressure due to pneumoperitoneum and manipulation of splanchnic vasculature, among others.^{1,4,40} Metabolic syndrome is related to an increase in plasmatic levels of fibrinogen and factors VII and VI, creating a potentially hypercoagulable status and an increase in plasminogen activator inhibitor-1 that reduces the conversion of plasminogen to plasmin, creating a hypo-fibrinolysis status.^{41,42} In addition to this, the increase in intra-abdominal pressure that carries the use of pneumoperitoneum can reduce splanchnic and portal flow, promoting clot formation.^{43,44} Surgical trauma to the superior mesenteric vein could be another explanation, but it is less likely because dissection is performed along the greater curvature far from this vessel. Nevertheless, mechanic and thermic action over the left gastroepiploic arch and short gastric vessels during dissection could be a leading factor.

Table 1 Demographics of patients

	Conventional thromboprophylaxis (n = 198)	PDTWPR (n = 223)	p-value
Age (years)	36,3 (11)	34,5 (10)	0.112
Sex (female/male)	135/63	141 / 82	0.286
Body mass index (kg/m ²) ^a	36.2 (2.67)	35.7 (3.39)	0.437
PMVT cases (n) ^b	4	0	< 0.05*
Bleeding episodes (n)	0	0	-

^a Data represent mean (standard deviation).
^b Common symptom: abdominal pain; diagnosis was confirmed with contrast-enhanced computed tomography.
 * Statistical significance.
 PDTWPR, post-discharge thromboprophylaxis with rivaroxaban.

Table 2 Characteristics of patients with portal and mesenteric venous thrombosis

Case	Age (year)	Sex	BMI (kg/m ²)	Comorbidities	Habits	Oral contraceptive	Operative time (minutes)	length of stay	Symptoms	Thrombosis extension	Thrombophilia study
1	44	F	36	(-)	(-)	(-)	60	3	Late vague abdominal pain	RPV	(-)
2	35	M	35.6	IR, DLP	T	(-)	70	2	Epigastric pain	RPV, LPV	(-)
3	19	F	36	IR	(-)	(+)	60	3	Epigastric pain	MPV, RPV, LPV, SV, SMV	Protein S deficiency
4	28	F	33.2	DM	A, T	(-)	75	3	Vague abdominal pain	MPV, RPV, LPV, SV, SMV	(-)

A, alcohol use; DLP, dyslipidaemia; DM, diabetes mellitus; F, female; IR, insulin resistance; LPV, left portal vein; M, male; MPV, main portal vein; RPV, right portal vein; SV, splenic vein; SMV, superior mesenteric vein; T, tobacco use

Direct oral anticoagulants have developed as effective and safe alternatives to vitamin K antagonist and LMWH. They have proven effective in preventing venous thromboembolism after orthopaedic surgery, for stroke prevention in patients with atrial fibrillation, and have been approved for the treatment of deep vein thrombosis and pulmonary embolism.^{9–17} There are also studies comparing the use of direct oral anticoagulants with LMWH for the prevention of venous thromboembolism in orthopaedic surgery where it is more effective in the prevention of venous thromboembolism after arthroscopy compared with enoxaparin, without increasing the risk of major bleeding.^{11–15} Data from meta-analyses and randomised trials of patients with venous thromboembolism report similar efficacy and reduced rates of bleeding when direct oral anticoagulants are compared with vitamin K antagonist.^{18–25}

A recent meta-analysis suggested that single thromboprophylaxis with rivaroxaban is more effective in the prevention of deep vein thrombosis in elective total knee replacement than combination strategies.⁴⁵ Rivaroxaban produces direct, selective and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways, inhibiting platelet activation and fibrin clot formation.^{14,15,46} Adverse effects have been reported in 6–8% of patients with hip replacement surgery who use 10mg once daily as prophylaxis for deep vein thrombosis, including anaemia and gastrointestinal bleeding.²¹ Patients with bleeding associated with direct factor Xa inhibitor anticoagulation cannot be dialysed.⁴⁷ For patients who are at risk, evidence suggests the use of andexanet alfa or an unactivated 4-factor prothrombin complex concentrates (if both are unavailable, a 3-factor prothrombin complex concentrate could be used.^{48,49} However, the use of these drugs has the potential to cause thrombosis, so they should be used only in cases of serious bleeding. Pharmacological safety and anticoagulation efficacy of direct oral anticoagulants in bariatric surgery have been described in small series and experimental studies but there is no published literature about the clinical safety and possible efficacy of the use of rivaroxaban for the prophylaxis of PMVT in patients who had laparoscopic sleeve gastrectomy.^{26–28} In our institution,^{5,50} the reported incidence of PMVT after sleeve gastrectomy is around 0.99%, similar to the reported international rate of 0.1–1.8%.^{1,3,5–8,31,32,35–38}

The main limitations of this study are that it is not a randomised prospective study and the small number of patients. Of note, there is a current clinical trial investigating the use of rivaroxaban as thromboprophylaxis in bariatric surgery.⁵¹ Data could be not complete as many patients may have had asymptomatic mesenteric venous thrombosis and may not have had a CT for diagnosis if they did not present to with abdominal pain. We do not have data on how many patients presented with abdominal pain, had a CT and had no PMVT noted.

The main strengths of the study are the strict monitoring of patients, the standardised surgical technique and that the postoperative care was the same for both groups (the same time of mechanical prophylaxis, LMWH prophylaxis, analgesic drugs and oral intake regimen).

No consensus exists on the choice, dosing or duration of thromboprophylaxis after bariatric surgery, with ranges that vary from 7 to 30 days.^{1,4,52,53} None of our patients who underwent laparoscopic sleeve gastrectomy and were placed on 13–14 days' thromboprophylaxis (enoxaparin 40mg once daily on the day of surgery and during the whole hospital stay and additional rivaroxaban 10mg once daily for 10 days after discharge) developed clinical PMVT. We therefore postulate that post-discharge thromboprophylaxis is essential in decreasing the incidence of PMVT, and rivaroxaban seems to be effective and safe in selected patients. We recommend using it with caution in patients with moderate or severe renal impairment (creatinine clearance <50ml/minute) when used for post-surgical venous thromboembolic prophylaxis. However, considering the average time of post-surgical PMVT development reported in most studies (10–20 days),^{1,5,6,54} perhaps we could use post-discharge thromboprophylaxis with rivaroxaban for a longer time in selected patients with a very high risk of venous thromboembolism in the future.

Conclusions

PMVT is an infrequent but serious complication of laparoscopic sleeve gastrectomy. In this study, the proportion of PMTV was significantly higher in patients who did not receive additional post-discharge thromboprophylaxis with rivaroxaban. Thromboprophylaxis during the whole hospital stay (two to three days) followed by rivaroxaban 10mg once daily for 10 days after discharge (completing in total 13–14 days of prophylaxis), could reduce the incidence of PMVT without an increase in bleeding complications. However, additional randomised prospective studies are needed to confirm these findings.

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