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Editorial

What is the optimal treatment of superior mesenteric vein/portal vein thrombosis after bariatric surgery? Is SMA-directed t-PA the answer?

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Acute thrombosis of the portal vein (PV) and superior mesenteric vein (SMV) is a relatively rare but insidious and potentially lethal abdominal complication. Unlike arterial thrombosis, the clinical line of demarcation is often not distinct for venous thrombosis. However, with the advent of readily available, highly sensitive, specific diagnostic modalities, it is now diagnosed at an earlier stage non-invasively. Moreover, the mortality has decreased due to this earlier diagnosis and treatment.

Recently, there has been a statistical significant increase in the number of PV thrombosis (PVT)/ SMV thrombosis (SMVT) after bariatric surgery. A precise explanation for this problem is still unclear; however, there are many hypotheses attempting to explain the mechanism of venous thrombosis after bariatric surgery. It is well established that obesity predisposes to venous thrombosis by reduction of fibrinolysis, elevation of clotting factors, and release of proinflammatory mediators [1]. Similarly, laparoscopy bariatric surgery increases intra-abdominal pressure with the requisite pneumoperitoneum; this results in decreased portal venous blood flow, which could lead to a relative prothrombotic environment [2,3]. Some bariatric patients are relatively dehydrated because of postoperative reduced fluid intake with the reduction of gastric capacity [4].

Heparin anticoagulation is still the most common treatment of PVT and SMVT; however, it has a failure rate exceeding 65% [5–7]. In partially occluded or nonoccluded vessels, heparin can facilitate exposure of the thrombus to endogenous plasmin. However, in the setting of complete occlusion, activated plasmin is shunted away from the thrombus. Thus, even systemic anticoagulation as well as systemic tissue plasminogen activator (t-PA) both have high failure rates in cases of high-grade partial or complete occlusion of portal flow [8]. The acute and chronic sequelae of portal vein occlusion are usually disabling and even fatal. Since the overall mortality rate is high for traditional anticoagulation and with limited use of systemic anticoagulation and t-PA, the management of PVT and SMVT remains a great clinical challenge.

The failure rate also increases with delayed diagnosis, more organized thrombosis and a greater extent of mesenteric venous involvement. It is therefore very important that the therapeutic options be guided by the extent of thrombosis; PV patency should be the treatment goal in these patients [8]. This study describes the effectiveness, safety, and clinical outcomes of 2 patients treated with catheter directed t-PA by route of superior mesenteric artery (SMA) for acute PVT and SMVT after weight loss surgery.

Methods

The charts of more than 4000 patients who underwent any type of weight loss surgery (band, gastroplasty, gastric bypass, sleeve gastrectomy, duodenal switch, and revisional surgeries) from a single practice were reviewed. These patients were operated between 2009 and 2016. Eight patients were identified with PVT and SMVT after weight loss surgery. The ninth patient was referred from another center. The average age was 45.4 years, and average body mass index (BMI) 46.8 was kg/m^2. The patient demographic characteristics are seen in Table 1. There were 7 documented cases of PVT and SMVT after laparoscopic sleeve gastrectomy (LSG) and 2 cases after laparoscopic loop duodenal switch surgery (LDS). Using standardized perioperative and postoperative protocols, two surgeons in our group performed all cases. The referred patient had undergone a very similar surgery (LSG). All patients

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Table 1
Patients' demographic characteristics

Patient number	Type of surgery	Age	Sex	BMI (kg/m²)	Co-morbidities	Operative time (min)	Length of stay (d)
1	LSG	45	M	45	OA	35	2
2	LSG	48	F	47	OA, GERD, OSA	30	2
3	LSG	56	M	42	MI, CABG, DVT, HTN, OSA, GERD	31	2
4	LSG	38	F	45	None	32	2
5	LSG	58	F	50	———	———	———
6	LSG	51	M	51	T2D, HTN, OSA, HL, DVT	32	1
7	LDS	30	M	47	COPD, OSA, HL, PE	71	2
8	LSG	39	M	37	OSA, HTN	30	1
9	LDS	44	F	58	HTN, Venous stasis	62	2

BMI = body mass index; LSG = laparoscopic sleeve gastrectomy; OA = osteoarthritis; GERD = gastroesophageal reflux disease; OSA = obstructive sleep apnea; MI = myocardial infarction; CABG = coronary artery bypass grafting; DVT = deep vein thrombosis; HTN = hypertension; T2D = type 2 diabetes; HL = hyperlipidemia; COPD = chronic obstructive pulmonary disorder; PE = pulmonary embolus; LDS = laparoscopic loop duodenal switch surgery

Patients 1–4 and 6–9 denied smoking and family history of thrombosis. We cannot comment on patient 5 as she was referred from another institution.

received deep vein thrombosis prophylaxis according to the consensus recommendation of 2008 [9]. The protocol included perioperative heparin (5000 U subcutaneously every 8 hr) and sequential compression device hose. All patients underwent uncomplicated LSG or LDS in reverse Trendelenburg with carbon dioxide insufflation pressure <15 mm Hg. The patients received postoperative fluids to maintain a urine output >60 mL/hr. Early ambulation was required. Patients were discharged by the second or third postoperative day taking adequate oral fluids (>2 L/d).

The patients presented to the emergency room (ER) on average of 15 days after surgery. Patient complaints were subtle and nonspecific including malaise, nausea, and abdominal pain; one patient did complain of fever. In all of the patients, diagnosis was established with a contrast-enhanced abdominal computed tomography (CT) scan occasionally preceded by duplex ultrasound of the portal venous system. Subsequent CT angiograms were performed at least once postoperatively to evaluate the status of the thrombus. All patients received systemic therapeutic heparin initially. Further treatment was determined by the severity of disease and extent of the thrombosis. All patients received long-term anticoagulation therapy with warfarin or preferably a factor Xa inhibitor (rivaroxaban, apixaban; minimum of 6 mo) as recommended by our consulting hematologist. All patients were evaluated for hemophilia.

Of 9 patients, only 2 patients received SMA catheter-directed t-PA treatment, 4 received anticoagulation alone, and 3 patients received portal vein thrombectomy facilitated by intraoperatively t-PA directly infused into a portal venous system.

SMA catheter-directed t-PA technique

The right femoral artery was cannulated using the Seldinger technique and a 6-Fr sheath (Terumo Medical Corp., Somerset, NJ) was placed. A 5-Fr diagnostic catheter (Cook Medical, Bloomington, IN) was angiographically placed into the SMA. The mesenteric circulation was imaged, confirming the degree of thrombosis. T-PA infusion was commenced through the SMA catheter at 1 mg/hr. Heparin drip was switched to the sheath side port and infused at 300–400 U/hr. No attempt was made to achieve a therapeutic-activated partial thromboplastin time (aPTT).

Case Report

Clinical findings and management of the first 7 patients can be seen in Table 2. (We have previously published the case report of our first 5 patients [8].)

Case 1

This patient is a 39-year-old male with sleep apnea, hypertension, and hyperlipidemia who underwent a LSG for morbid obesity (weight: 316.9 pounds, BMI: 36.6 kg/m^2). His surgery was without complication, and he was discharged home the same day of his surgery.

Two weeks post-LSG, this patient presented to the ER with sharp, shooting, mid-abdominal pain, malaise, nausea, and vomiting. His blood pressure was 170/80 on admission. His temperature was normal. He had normal white blood cell count (WBC) (8900/mm^3), high alanine transaminase (67 U/L) and high prothrombin time (12.7 s). The CT scan found occlusive thrombosis of SMV and branches of PV with mesenteric edema. Splenic vein was patent. Patient was initially started on therapeutic heparin drip of 9000 U bolus and then 200 U/hr continuous with a target of aPTT 2–2.5 times baseline (60–80 s). Since subsequent CT scans on days 2 and 4 did not show any resolution of the clot, we electively decided to place an SMA catheter under interventional radiologist and continuously infuse t-PA at 1 mg/hr with a systemic heparin drip at 300 U/hr. We then titrated t-PA to 1.5 mg/hour and continued heparin drip for next 3 days. The patient had complete resolution of the clot on subsequent CT scan and was later discharged on oral

Table 2
Clinical findings and management of first 7 patients

Patient number	Laboratory evaluation	Radiological evaluation	Management	LOS	Outcome
1	Normal	Nonocclusive PVT	• Heparin drip for 2 d.	2	Complete resolution of clot.
2	WBC: 10,700/mm^3	Stable nonocclusive PVT	• Heparin drip for 5 d. • Subsequent CTA found small bowel thickening but stable nonocclusive thrombus.	6	25 d later, patient presented with bowel perforation requiring bowel resection and postoperative anticoagulation.
3	WBC: 16,000/mm^3, sr. lactate: 4 mmol/L	Partial PVT, occlusive SMVT, ascites, and ischemic bowel	• Portal–SMV thrombectomy facilitated by t-PA infused directly into portal system, followed by heparin drip and small bowel resection.	11	Patent portal system.
4	WBC: 13,000/mm^3, ALT: 180 U/L	Occlusive PVT, SMVT, SVT, ascites, and bowel wall thickening	• Portal–SMV thrombectomy facilitated by t-PA infused directly into portal system, followed by heparin drip.	14	SV and left hepatic vein remained thrombosed but no evidence of portal hypertension. Patient had excellent portal flow.
5*	————	Occlusive PVT	• Heparin drip was started but in next 30 hours, she deteriorated and developed MOF. • She was then transferred to our facility where PV thrombectomy was done.	3	In spite of successfully reestablishing portal flow, she died in 3 days because of MOF.
6	CRP: 22.5 mg/L, Glucose: 127 mg/dL	Stable occlusive SMVT & nonocclusive PVT and SVT	• Heparin drip for 5 days	6	Persistent occlusion of SMVT, but PV and SV were patent.
7	WBC: 11,990/mm3, Lipase: 380 U/L, ALT: 129 U/L	Nonocclusive PVT & partially occluded SVT	• Rivaroxaban (Xarelto)	1	Complete resolution of the clot with patent PV, SV, and SMV

LOS = length of stay; PVT = portal vein thrombosis; WBC = white blood cell count; CTA = CT angiogram; SMVT = superior mesenteric vein thrombosis; SMV = superior mesenteric vein; t-PA = tissue plasminogen activator; SV-splenic vein; MOF = multi-organ failure; PV = portal vein; CRP = C-reactive protein; SVT = splenic vein thrombosis; ALT = alanine transaminase.
*This patient was referred from another center.

anticoagulation. He has had no symptom recurrence after 6 months' follow-up.

Case 2

This patient is a 44-year-old female with history of hypertension and venous stasis who underwent LSG surgery for morbid obesity (weight: 360.3 pounds, BMI: 58.15 kg/m^2). Postoperatively, the patient had difficulty tolerating the oral fluids. She was given intravenous hydration for an additional 24 hours and then discharged with adequate fluid intake.

On the 10th postoperative day, the patient presented to ER with nausea, vomiting, and severe upper epigastric pain. Her vital signs were normal; lab work included WBC: 13,000 and alkaline phosphatase: 121, but the other values were normal including amylase and lactate. A CT angiography revealed extensive thrombus in the SMV, occlusive thrombus in the main PV, and occlusive thrombus in the left PV. The patient was immediately started on a therapeutic heparin drip for 24 hours. The subsequent CT scan did not show significant improvement compared with the previous scan. The patient was therefore treated with t-PA continuously infused by a SMA catheter at 1 mg/hr along with systemic heparin at 400 U/hr. Two days later, the CT scan found nonocclusive thrombus in the main portal vein and residual thrombus in the left PV. Due to miscommunication between the surgical department and interventional radiologist, the SMA catheter was pulled out prematurely. As a result, the patient was put on systemic anticoagulation. Symptomatically the patient had improved but did not have resolution of the clot. This patient was discharged on Eliquis, 5 mg twice daily. Her symptoms gradually improved.

Discussion

Portal and mesenteric vein thrombosis is associated with high morbidity and even mortality. Complications ranges from immediate bowel infarction to long-term problems associated with portal hypertension. Obesity itself is a hypercoagulable state associated with increased thrombotic events [10]. All patients undergoing bariatric surgery carry this risk [11]. There is an increased significant increase risk of PVT after LSG compared with other bariatric procedures or other abdominal procedures [12–14]. This is evident from our data. Most cases of PVT occur after LSG (7 of 9 patients). The precise reason is unclear.

Patients with PVT were present with nonspecific symptoms including nonspecific abdominal pain. A CT scan with intravenous contrast is indicated in all such patients [15]. Initial treatment with anticoagulation such as heparin is

urged for all indicated patients with demonstrable thrombus. Ultimate treatment is determined by disease severity. Our previous paper found that the distinction between non-occlusive, high-grade nonocclusive, and occlusive thrombosis should determine appropriate treatment [8]. Attempts to establish portal vein patency should be the goal of the treatment. Anticoagulation will usually not reestablish portal flow in patients with occlusive PVT [5]. Similarly, systemic t-PA fails in occlusive thrombosis since plasmin is shunted away from the clot. In such cases, catheter directed t-PA via SMA approach should be considered. This approach is effective in cases resistant to standard anticoagulation therapy [8]. This was also seen with our cases, where therapeutic heparin did not facilitate thrombolysis. In cases of high-grade or occlusive PVT, especially if bowel ischemia is likely, surgical thrombectomy with mesenteric venous catheter should be considered.

There have been reports about percutaneous transjugular/transhepatic thrombolytic therapy; however, this approach has met with limited success and is now rarely used. Infusion via an SMA catheter is the preferred route of administration of t-PA, as reported in the literature. Because both of our patients were hemodynamically stable with no strong clinical or laboratory evidence of infarcted bowel but with occlusive thrombus, we proceeded with thrombolytic therapy. There are many advantages of SMA catheter directed t-PA. The systemic dose of t-PA can be significantly reduced, while still delivering a higher mesenteric concentration with much better thrombolytic effect. The "first pass" is avoided, and the dilutional effect is significantly reduced. Less heparin is required still allowing excellent mesenteric anticoagulation because of reduced dilutional effect and reduced exposure to endothelial heparin binding, as opposed to systemic administration.

Furthermore, the mesenteric catheter easily facilitates serial CT portography, reducing the amount of contrast and potential renal toxicity.

SMV thrombosis normally starts in small venules of the mesentery and propagates into the SMV. Allowing infusion of t-PA via a catheter in the SMA allows the t-PA to infuse small mesenteric venous branches, which enables dissolution of thrombi within capillaries and venules. Direct catheter infusion of t-PA into the portal venous system only addresses larger and central thrombus, and it is technically more difficult with higher risk of bleeding.

Our second patient had incomplete resolution of thrombosis after 36 hours of SMA catheter-directed t-PA. In retrospect, longer treatment and higher dosing of t-PA would likely have rendered a better result. An alternative approach would have been catheter-directed thrombolysis via SMV + SMA. There have been many reports that show the favorable outcome of this combined route. However, there is again an increased risk of bleeding with this approach. We have titrated t-PA to 2–2.5 mg/hr along with heparin drip, carefully following patient response and lab work (PT/ PTT, liver functions, hematocrit, platelet count, WBC, fibrinogen, d-dimer, and lactate).

Currently there is no standard thrombolytic regimen for porto-mesenteric venous thrombosis. In our patients, treatment dosage and duration was determined by clinical judgment. One of the surgeons in our team has 25 years of experience with liver transplantation and portal vein thrombectomy in many different clinical presentations. Our goal has been aggressive pursuit to reestablish PV patency, to avoid disastrous acute and insidious long-term complications. We selected t-PA for both of our patients. T-PA has excellent thrombolytic effect, less plasminogen activation, less alpha2-antitrypsin consumption, and less fibrinogen breakdown compared with urokinase.

The main limitation of this study is that this is a small case series, and a strong recommendation for a single technique cannot be made. However, if PVT and SMVT is diagnosed before bowel ischemia occurs, SMA catheter-directed t-PA is an excellent alternative to surgical treatment. In more extreme cases of PVT, especially involving bowel ischemia, laparotomy with surgical thrombectomy and placement of transabdominal mesenteric venous catheter should be considered.

Conclusions

This paper emphasizes: (1) early diagnosis is very important for best patient outcomes; (2) therapeutic options such as anticoagulation, catheter-directed thrombolytic therapy, and portal vein thrombectomy should be based on the severity and extent of thrombosis; (3) catheter-directed mesenteric porto-venous clot perfusion with t-PA is useful in cases resistant to standard anticoagulation; and (4) the greater risk of systemic t-PA and exposure to the gastric staple line is avoided via SMA catheter-directed t-PA. The lower total dose of t-PA and heparin is reduced. T-PA and heparin limited to the mesenteric circulation help prevent systemic bleeding and achieve excellent mesenteric thrombolysis and anticoagulation. (5) T-PA should be titrated upward to 2– 2.5 mg/hr for more than 48 hours, carefully monitoring the patient. However, larger study populations utilizing much larger databases (such as the Michigan collaborative, SRC, MBSAQUIP) would be required to further evaluate the outcomes of this technique, assuming other surgeons are using this technique as well.

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Since this is a retrospective study, the formal consent is not required for this type of study. The authors have no commercial associations that might be a conflict of interest in relation to this article

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