# Old is gold, sometimes! Apixaban after Bariatric Surgery

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**Abstract**

A 39-year-old woman was admitted with right leg deep venous thrombosis (DVT). She was started on apixaban tablets but developed pulmonary embolism. The medical history showed sleeve gastrectomy. The failure of the antithrombotic drug shed light on the efficacy and pharmacodynamic changes of DOACs after bariatric surgery

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Abstract

A 39-year-old woman who was taking contraceptive pills was admitted with right leg deep venous thrombosis (DVT). She was started on apixaban tablets, and after 8 days, she developed proximal progression of DVT and pulmonary embolism. Her past medical history later showed a history of sleeve gastrectomy. The patient responded to a vitamin K antagonist after heparin. The failure of the antithrombotic drug shed light on the efficacy and pharmacodynamic changes of DOACs after bariatric surgery in the absence of commercially available blood monitoring tests.

**Key words** Apixaban, Bariatric Surgery, thromboembolism

**Key Clinical Message**

Bariatric surgeries lead to complicated changes in pharmacodynamics of DOACs.

The absence of clinical data on the efficacy of DOACs after various bariatric procedures make it difficult to justify their use after bariatric surgery

Case report

A 39-year-old woman with a 6-month history of oral contraceptive pills presented with left pain and mild swelling. There was no chest pain and no hemoptysis.

Doppler of the right leg showed a thrombus in the right distal popliteal vein up to the confluence of the peroneal and posterior tibial veins. ECG and echocardiography results were normal.

She was started on 10 mg apixaban bid for one week, which was decreased to 5 mg bid on day 8. This was followed on day 9 by increasing pain and extension of the swelling into the left thigh with difficulty breathing.

Physical exam showed the same swelling of the right lower limb, a weight of 104 kg, a BMI of 34 kg/m2, normal vital signs and normal O2 saturation in room-temperature air.

CT angiography showed an acute angled filling defect in the posterior and medial segmental arteries of the right lung lower lobe and subsequent subsegmental arteries. An acute angled filling defect was noted in the posterior segmental artery of the right lung upper lobe. The right ventricle/left ventricle ratio was 0.85.

Repeated Doppler of the right lower limb showed persistence of popliteal vein thrombosis with no recanalization. Cranial extension of the popliteal thrombus was noted in the distal superficial femoral vein at the adductor canal. Calf veins (muscular veins) were partially thrombosed in the proximal and mid-calf.

Upon direct questioning of the patient, she admitted bariatric surgery 4 years ago in another facility that was not mentioned in her previous medical records.

All her lab tests were normal, including CBC, ProBNP and troponin. The results of factor V Leiden mutation, prothrombin G20210A mutation, protein S deficiency, protein C deficiency, antithrombin deficiency and antiphospholipid syndrome were all negative.

The patient was started on heparin infusion for one week and was maintained on warfarin for 6 months, without any further adverse events or provoked attacks.

Discussion

Bariatric surgery encompasses a variety of procedures, including sleeve gastrectomy (SG), the most common bariatric procedure performed (51.7%); adjustable gastric banding (AGB); Roux-en-Y gastric bypass (RYGB); and biliopancreatic diversion with duodenal switch (BPD-DS) (1). Bariatric surgeries result in weight loss through 1) restriction of caloric intake by reducing the volume of the stomach (SG and AGB), 2) malabsorption by reducing the effective intestinal surface area (BPD-DS), or 3) a combination of restriction and malabsorption (RYGB and BPDDS).

Drug absorption will be affected after bariatric surgeries as well as bioavailability depending on the chemical properties of the drug (i.e., molecular size and solubility)(2) and on changes in the properties of the gastrointestinal tract (PH, intestinal flow time and surface area of absorption)(3).

Certain DOACs (rivaroxaban) require food to increase absorption and hence bioavailability, reaching $>$ 80% when administered with food (4). When undertaking restrictive diets after bariatric surgeries, the absorption of therapeutic rivaroxaban is reduced (4). This effect is not observed with other DOACs and warfarin. Dabigatran requires an acidic environment for absorption; therefore, (5) after bariatric surgery, the pH in the gastric pouch is more alkaline because of the reduced volume for gastric acid secretion, which could affect dabigatran dissolution and resultant absorption (6).

The anatomy of the gastrointestinal tract changes in different ways after different bariatric surgeries, which may affect the location of drug absorption; in the absence of dedicated studies, indirect evidence can be utilized, such as the location of drug absorption (table 1). For example, apixaban is primarily absorbed in the proximal small intestine, with some gastric absorption (7,8); dabigatran is absorbed in the lower stomach

and duodenum (9); edoxaban is absorbed in the proximal small intestine(10); and rivaroxaban is primarily absorbed in the proximal small intestine, with some gastric absorption(11).

The use of DOACs in the setting of postbariatric surgery is not supported by enough literature. One case reported the successful use of rivaroxaban following bariatric surgery with a high venous thromboembolism risk, and the anti-Xa levels were monitored (12). In a total of 6 patients who underwent sleeve gastrectomy (SG) and 6 patients who underwent Roux-en-Y-gastric bypass (RYGB), the pharmacokinetic and pharmacodynamic parameters were assessed and compared with those in patients prebariatric surgery; the type of surgery did not appear to affect the pharmacokinetics or pharmacodynamics of 10 mg prophylactic rivaroxaban once daily, which was well tolerated and considered safe in this trial (13). For apixaban, there is no approved dosing for obese patients, especially when considering surgical interventions such as bariatric surgery. There is an ongoing study (ClinicalTrials.gov Identifier: NCT02406885) to determine the durability or changes in the pharmacokinetics and pharmacodynamics of apixaban in patients with a body mass index (BMI) of 35 kg/m2 or greater following one of two bariatric surgical procedures (preoperative versus postoperative vertical sleeve gastrectomy or Roux-en-Y gastric bypass patients).

Our case report showed that in the absence of other causes of apixaban failure, a history of SG might cause subtherapeutic levels of the drug, leading to the progression of DVT and pulmonary embolism. The complicated changes in PKs/pharmacodynamics (PDs) and the absence of clinical data on the efficacy of DOACs after various bariatric procedures as well as the lack of widely available monitoring tests for DOACs make it difficult to justify their use after bariatric surgery. On the other hand, as the anticoagulant effect of warfarin can be routinely monitored, it is the preferred agent to use in patients after bariatric surgery. If DOACs must be used in patients after bariatric surgery, we suggest checking the drug-specific peak and trough levels. If the drug-specific level is not within the expected range, then VKA should be used.

Conclusion

There is little literature available on the effects of bariatric surgery on therapeutic anticoagulation. The changes in drug disposition after bariatric surgery are not predictable without independent studies of individual drugs. At present, it appears most prudent to use a vitamin K antagonist rather than a DOAC for therapeutic oral anticoagulation after bariatric surgery, as VKAs can be easily monitored, and the dose can be easily adjusted.

*Ethical/consent statements:*The ethical board of Ahmadi hospital, Kuwait, had approved the case report , and the concerned patient had been given full information and consent gave for the case report publication

Contribution

Zouheir I Bitar wrote the article, Ossama S. Maadarani shared in the discussion and with M Mohsen and N **Alkazemi** in collecting the data and revision of the manuscript

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Table 1 Location of absorption of Antithrombotic Agents

| Agent | Location of Absorption |
|---|---|
| Apixaban | Primarily the proximal small intestine; some gastric absorption |
| Dabigatran | Lower stomach and duodenum |
| Edoxaban | Proximal small intestine |
| Rivaroxaban | Primarily the proximal small intestine; some gastric absorption |
| Warfarin | Proximal |

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