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ORIGINAL ARTICLE

Dabigatran (Pradaxa) Is Safe for Extended Venous Thromboembolism Prophylaxis After Surgery for Pancreatic Cancer

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Abstract

Background The American College of Chest Physicians and American Hepato-Pancreato-Biliary Association recommend using low-molecular-weight heparin for 28 days postoperatively for venous thromboembolism prophylaxis after cancer surgery. Dabigatran is a once daily oral anticoagulant that is FDA approved for venous thromboembolism prophylaxis after orthopedic surgery, uses fixed dosing, and has an antidote.

Methods Patients undergoing surgery for malignant pancreatic tumors (neuroendocrine excluded) from January 2017 to January 2018 were converted to dabigatran 220 mg daily on discharge until postoperative day 28; patients with medical or insurance contraindications were converted to enoxaparin or another direct oral anticoagulant. The primary endpoint was bleeding complications through 90 days.

Results A total of 134 patients were considered for this study (median age 67 ± 10; 58.9% male). Eighty-seven (82.9%) patients received dabigatran and 18 (17.1%) received another form of anticoagulation. There were 19 (4.2%) patients not prescribed dabigatran due to medical or inpatient contraindications. Four patients experienced bleeding complications after discharge while on dabigatran. Two (2%) were major bleeds (Clavien-Dindo IV and V), and 2 (2%) were minor (Clavien-Dindo I). Patient compliance was excellent, with 93% of prescribed patients fully completing their prophylaxis. There were 2 patients that developed symptomatic deep vein thrombosis.

Conclusion The use of a direct oral anticoagulant as extended venous thromboembolism prophylaxis after major gastrointestinal surgery has not been studied to date. These results show dabigatran to be a safe alternative to low-molecular-weight heparin for extended venous thromboembolism prophylaxis with regard to bleeding complications.

Keywords Venous thromboembolism · Dabigatran · Postoperative hemorrhage · Pancreas · Quality improvement · Surgical oncology

Introduction

The risk of venous thromboembolism is 4–6.5 times greater in cancer patients and increases with chemotherapy and radiotherapy.[1–6] Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading causes of mortality and morbidity in patients undergoing major abdominal or pelvic surgery.[2–7] The American College of Chest Physicians and American Hepato-Pancreato-Biliary Association recommend the use of low-molecular-weight heparin (LMWH) for 28 days postoperatively to prevent VTE after cancer operations,[8,9] because at least 30 to 50% of postoperative VTE events occur in the outpatient setting.[10,11]

The efficacy of postoperative VTE prophylaxis has been well documented. One study found the rate of VTE

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decreased from 12.0 to 4.8% when comparing enoxaparin to placebo.[12] Another study found the incidence of VTE decreased from 16.3% with short-term prophylaxis of 7 days to 7.3% with extended prophylaxis of 28 days.[13] Despite strong evidence, these guidelines have not been widely adopted in to clinical practice. Less than half of cancer patients undergoing abdominal surgery received perioperative VTE prophylaxis and there is large variation in VTE prophylaxis across hospitals.[14] Another study found only 27% of patients received a prescription for extended prophylaxis following major cancer surgery.[15] This is likely a consequence of prescriber and patient inconvenience.

Direct oral anticoagulants (DOACs) have been approved by the Food and Drug Administration (FDA) for VTE prophylaxis following orthopedic procedures, and oral edoxaban has recently been shown to be equivalent to subcutaneous LMWH dalteparin for treatment of cancer-associated VTE.[16] Unlike LMWH, DOACs do not require injection with associated patient aversion and discomfort. And in contrast to warfarin, DOACs do not require laboratory monitoring and dose adjustments, which may be complicated by varying diet after pancreatic surgery. There remains consternation around the inability to reverse DOACs for bleeding or urgent procedures. However, dabigatran has an effective, FDA-approved antidote.

The use of a DOAC as extended VTE prophylaxis after major abdominal surgery has not been studied to date. The aim of this study was to determine the safety of dabigatran for extended postoperative VTE prophylaxis with respect to bleeding complications after surgery for pancreatic adenocarcinoma.

Materials and Methods

After approval from the institutional review board and in compliance with Health Insurance Portability and Accountability Act regulations, a prospective quality improvement program for extended VTE prophylaxis was initiated in January 2017 and studied through January 2018. Patients received heparin 5000 units subcutaneous prior to induction of general anesthesia, and continued twice or thrice daily to discharge. This was standard practice dating to 2006 and was followed even when operations involved venous or arterial procedures. Patients undergoing resection of malignant pancreatic tumors (neuroendocrine excluded) were prescribed dabigatran 220 mg daily from date of discharge through postoperative day 28 unless medically contraindicated. No routine exemptions were made for patients that had undergone vascular resections or reconstructions, or irreversible electroporation. Enoxaparin or DOACs were supplemented for insurance or medical reasons. No patient was prescribed warfarin. Patients were not prescribed dabigatran if they were on clopidogrel, had postoperative lengths of stay greater than 28 days, or had medical contraindications including creatinine clearance < 30 mL/min or mechanical prosthetic heart valves. Clopidogrel is neither contraindicated with dabigatran nor approved for VTE prophylaxis, but was an exclusion factor in this program given the primary endpoint. Although not directly related to our patient population, this decision was based on the packet insert which cautioned against the use of dabigatran and platelet inhibitors in patients undergoing neuraxial anesthesia or undergoing spinal puncture. There have been reports of dabigatran causing thrombocytopenia in post marketing experience. We cannot speak to this, as post-discharge labs were only ordered as needed. Patients were given pre-discharge instruction by trained medical personnel about extended VTE prophylaxis.

All prescriptions were submitted electronically. Patients were seen in the office at least 1, 3, and 5 weeks post-discharge, and medication reconciliation was performed. Routine screening for VTE was not performed. Perioperative complications were prospectively logged in an IRB-approved database.

Extended VTE prophylaxis was considered successful if patients completed 28 days of VTE prophylaxis. The primary endpoint was any bleeding complications through postoperative day 90 and was graded according to the Clavien-Dindo classification.

Results

A total of 248 patients underwent pancreatic resection during implementation of the quality improvement program. Of these, 134 patients had non-neuroendocrine, malignant pancreatic tumors and were the focus of this study. The median age was 67 ± 10 years old, and the majority of patients were male (58.9%) (Table 1). Fifteen patients had borderline resectable disease and 13 had locally advanced pancreatic cancer based on preoperative imaging. Overall, 18 patients underwent neoadjuvant chemotherapy, 14 received FOLFRINOX, and 4 received gemcitabine and abraxane. Fourteen patients received stereotactic body radiation therapy, and 1 patient received intensity-modulated radiation therapy.

Pancreaticoduodenectomy (Whipple) was the most commonly performed procedure (88, 65.6%), followed by distal pancreatectomy (32, 23.8%), irreversible electroporation with Whipple or distal pancreatectomy (11, 8.2%), total pancreatectomy (2, 1.5%), and Appleby procedure (1, 0.7%). Vascular resection and reconstruction of the superior mesenteric or portal vein occurred in 29 (21.6%) of cases. This included 10 longitudinal suture repairs, 10 end-to-end anastomoses, 5 internal jugular interposition grafts, and 4 repairs

Table 1 Patient demographics and procedure details

	Total $n = 134$
Demographics	
Age, mean ± SD	67 ± 10
Male/female (%)	59/41
BMI, mean ± SD	26 ± 5
Pathology	
Pancreatic adenocarcinoma	100
Cholangio-, duodenal, or ampullary carcinoma	14
Pancreatic adenocarcinoma arising from IPMN	12
Other, pancreatic malignancies (non-PNET)	8
Operation	
Whipple	88
Distal	32
Nanoknife ± Whipple or distal	11
Total	2
Appleby	1

with gonadal vein patches. Five (3.7%) arterial repairs, reconstructions, or ligations were performed: (1) superior mesenteric artery reconstruction with interposition synthetic graft after partial transection during a Whipple; (2) aortic to proper hepatic artery reverse saphenous vein graft in a patient undergoing a Whipple who had previously undergone an Appleby procedure; (3) suture repair of a small diameter splenic artery injury during a Whipple that extended to the left of the celiac axis; (4) Appleby after neoadjuvant chemotherapy and radiation; (5) resection of the common and proper hepatic artery in a patient with a replaced right hepatic artery during a Whipple.

Prolonged VTE Prophylaxis

There were 105 (78.4%) patients prescribed prophylactic anticoagulation through postoperative day 28 (Fig. 1). Of these, 87 (82.9%) patients received dabigatran and 18 (17.1%) received another form of anticoagulation: enoxaparin ($n = 12$), rivaroxaban ($n = 3$), and apixaban ($n = 3$). Prescriptions for anticoagulants other than dabigatran were most often because of insurance coverage. Dabigatran was started at median of 7 (IQR 5, 10) days postoperatively. There were 8 (5.9%) patients with inpatient complications not given dabigatran. This included 6 (4.5%) patients who were inpatient > 28 days postoperatively (Clavien-Dindo II–IV) and thus completed their prophylaxis while in the hospital and 2 (1.5%) patients that had bleeding complications postoperatively (Clavien-Dindo II/IIIb). Both of the latter patients were taken back to the operating room for bleeding and not prophylaxing for the full 28 days was at the discretion of the treating physician. Both had resectable disease, and neither had vascular reconstructions.

There were 11 (8.2%) patients who were not prescribed extended prophylaxis because of medical contraindications including end stage renal disease (1), coagulopathy from liver disease (1), mental impairment and risk of injury (1), mechanical heart valve (1), or preoperative clopidogrel (7). Additionally, 2 (1.5%) patients could not get insurance approval for prolonged VTE prophylaxis. There was 1 (0.7%) patient who expired postoperatively while still inpatient (Clavien-Dindo V). This patient (Charlson Comorbidity Index = 4) had resectable disease on preoperative imaging and did not undergo neoadjuvant therapy. The patient underwent superior mesenteric artery reconstruction with an interposition synthetic graft after partial transection, and passed from multisystem organ failure. There were 7 (5.2%) eligible patients not prescribed dabigatran because of staff oversight.

Bleeding Events

There were 4 patients that experienced outpatient bleeding complications while on dabigatran. There were 2 (2%) major arterial bleeds: rupture of a splenic artery pseudoaneurysm in a patient who underwent an extended Whipple with primary repair of a splenic artery injury (Clavien-Dindo IV) and rupture of a double clip-ligated common hepatic artery stump (Clavien-Dindo V) after a Whipple with resection of the common and proper hepatic artery in the presence of a replaced right hepatic artery. The former patient had renal cell carcinoma and did not receive neoadjuvant therapy, whereas the latter patient received neoadjuvant chemoradiotherapy with gemcitabine and abraxane and had a Charlson Comorbidity Index = 9. The remaining 2 (2%) bleeding complications were minor: hematuria and lower gastrointestinal bleeding, both Clavien-Dindo I; neither received neoadjuvant therapy. There were 2 confirmed cases of DVT while on dabigatran; both patients were subsequently administered therapeutic dabigatran. There were no bleeding events in the 18 patients that received enoxaparin, rivaroxaban, or apixaban, yet this was not statistically significantly relative to dabigatran ($p = 0.83$).

Patient compliance was high, with 93% (7/101) of prescribed patients not suffering a bleeding complication fully completing their prophylaxis.

Discussion

Patients with cancer and VTE have a worse prognosis than patients with cancer alone, and VTE is one of the leading causes of death in these patients. Current VTE prophylaxis guidelines recommend 28 days of LMWH for patients after liver or pancreas resection. An extended VTE prophylaxis quality improvement program for patients undergoing surgery for pancreatic adenocarcinoma was implemented. It was

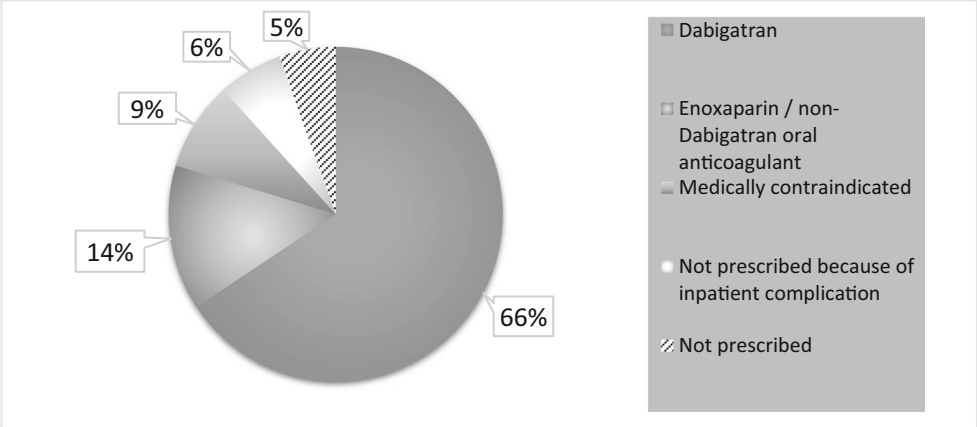

Fig. 1 Prophylactic anticoagulation to postoperative day 28

hypothesized that a once-daily, fixed-dose, oral anticoagulant would be embraced by patients and physicians. These qualities overcome common barriers to extended prophylaxis, such as patient discomfort with injectables and individualized dosing.[17,18] Dabigatran, a rapid-acting competitive and reversible direct inhibitor of thrombin, was chosen because it is approved by the FDA for VTE prophylaxis after orthopedic procedures and has an effective reversal agent should excessive bleeding occur. The latter was essential, as physicians remain concerned about the risk of severe bleeding with anticoagulants following major abdominal surgery, despite current evidence suggesting protection against VTE outweighs the risks of excessive bleeding.[19–21]

There were 105 (78.4%) patients prescribed prophylactic anticoagulation through postoperative day 28. The post-discharge bleeding complication rate on extended VTE prophylaxis was 3.8%. There were no statistically significant differences based on whether venous or arterial reconstructions, resections, or ligations were performed. Additionally, there were no statistically significant differences based on whether patients received dabigatran, enoxaparin, or another DOAC. These results are also consistent with those of other studies investigating safety and efficacy of VTE prophylaxis in surgical patients. Prospective trials analyzing the safety and efficacy of postoperative enoxaparin after oncologic abdominal surgery reported 2.9–9.2% of patients developing postoperative bleeding.[22,23] A study investigating 349 patients who underwent major hepatobiliary-pancreatic surgery found an increased rate of overall bleeding between the prophylaxis and no intervention groups (26.6% vs 8.5%). However, this study also found no significant difference in the rate of major hemorrhage requiring blood transfusion or hemostatic intervention.[24] Importantly, implementation of this program at our institution was not associated with a significant difference in readmissions for postoperative bleeding or major/minor bleeding events compared to 2016.

Previous studies have found adherence to prophylactic anticoagulation regimens to range from 13 to 81%, with patient education, injections, and type of ward at discharge affecting compliance.[25–28] Patient adherence and satisfaction are demonstrably higher with oral regimens over subcutaneous ones.[29] As such, we predicted a once-daily oral anticoagulant would be acceptable to patients for extended prophylaxis. Indeed, this was found to be the case: upon follow-up of all patients capable of completing a 28-day course of VTE prophylaxis, 93% of patients reported fully completing their prophylaxis. The specific reasons why patients voluntarily terminated prophylaxis could not be elucidated. There were 7 eligible patients not prescribed dabigatran upon discharge in violation of the protocol. After reviewing medical records, these oversights were attributed to personnel error during adoption of the program, and not physician discretion. The number of enoxaparin and other DOAC prescriptions (17.1%) reveals challenges in non-uniform insurance coverage. However, only 2 patients could not get coverage for any form of extended prophylaxis, which suggests against insurance being the limiting factor in greater acceptance. Admittedly, measurable in- and outpatient resources were sometimes required to identify a covered option. Perhaps this and further investigations will affect insurer practices, as DOACs offer particular benefits to patients undergoing gastrointestinal surgery at high risk for VTE complications.

This study was limited in that dabigatran was not compared to alternative anticoagulant agents with regard to patient compliance and efficacy of VTE prevention. However, the objective was to determine the safety of dabigatran for extended postoperative VTE prophylaxis with respect to bleeding complications. These preliminary findings support design of a more resource-intensive, randomized controlled trial of DOAC versus LMWH for VTE prophylaxis in patients undergoing major oncologic gastrointestinal surgery. This study would need to survey for VTE preoperatively, and after 28 days of prophylaxis. Hemorrhage can be common after pancreatic operations and is at the root of a large proportion of related mortality. As a consequence, dabigatran was not started immediately postoperatively. Given the low bleeding risk, starting dabigatran earlier in place of injectable heparins

is warranted, as is consideration of other DOACs. However, given the morbidity associated with pseudoaneurysms and that 2 of 4 patients taking dabigatran after arterial interventions bled (1 fatally), further study and caution are indicated in this circumstance.

In conclusion, this is the first study of extended VTE prophylaxis following oncologic gastrointestinal surgery utilizing a direct oral anticoagulant. These findings suggest dabigatran is safe for extended VTE prophylaxis with regard to bleeding complications after pancreatic surgery, and patient compliance is excellent.

Author Contribution All authors contributed to the conception or design of the project; assisted with acquisition, analysis, or interpretation of data; drafted and/or revised the manuscript, and had final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity may be resolved.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

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