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Implementation of extended prolonged venous thromboembolism prophylaxis with rivaroxaban after major abdominal and pelvic surgery – overview of safety and early outcomes

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Manuscript Preparation
E – Literature Search
F – Funds Collection

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ABSTRACT:

Purpose: Venous thromboembolism (VTE) after colorectal surgery is a well-documented complication, resulting in a general recommendation of extended post-discharge prophylaxis. Rivaroxaban, a factor Xa inhibitor, is a daily tablet approved for treatment of VTE and prophylaxis after orthopedic surgery.

Aim: The purpose of this study is to evaluate the safety of rivaroxaban for extended prophylaxis after major abdominal and pelvic surgery.

Methods: This is a retrospective review of patients undergoing major colorectal surgery at a regional hospital in Kiev, Ukraine. Patients received peri-operative VTE prophylaxis with subcutaneous heparin and then transitioned to rivaroxaban for a total of 30 days. Occurrences of major or minor bleeding, blood transfusion, and a need for re-intervention were noted. Phone surveys were administered on post-operative day 30 to assess compliance and satisfaction with the regimen.

Results: A total of 51 patients were included in the study with an average age of 62.4 years. Seventy-one percent of the cases were abdominal, 29% were pelvic cases and 59% were done laparoscopically. There was one episode of major intra-abdominal bleeding requiring return to the operating room. There were 2 minor bleeding episodes which did not require intervention. There were no VTE events in the group. The phone survey response rate was 100%. All but one patient reported having completed the full course of rivaroxaban. Patients reported that oral prophylaxis was easy to adhere to and preferable compared to injections.

Conclusion: Implementation of extended prophylaxis with rivaroxaban is easy, safe and does not increase rates of post-operative bleeding.

KEYWORDS: colorectal surgery, Rivaroxaban, venous thromboembolic events, VTE

ABBREVIATIONS

ACCP – American College of Chest Physicians
ASCRS – American Society of Colon and Rectal Surgeons
CAD – coronary artery disease
CHF – congestive heart failure
DVT – deep vein thrombosis
NICE – National Institute for Health and Care Excellence
PE – pulmonary embolism
VTE – Venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE) is a frequent complication in both medical and surgical patients with substantial associated morbidity and mortality [1, 2]. The rate of VTE events, including deep vein thrombosis (DVT), pulmonary embolism (PE) and portal vein thrombosis, is higher among patients undergoing major abdominal or pelvic surgery [3]. Risk factors for post-operative VTE include advanced age, malignancy, inflammatory bowel disease, pelvic surgery, prolonged immobilization, lithotomy position during surgery and obesity. The aforementioned risk factors are all common in colorectal surgery [4]. Given these variables, it is not surprising that colorectal surgery patients are at high risk for developing VTE [4, 5].

An increasing body of evidence in recent years now favors an extended duration of post-operative VTE prophylaxis in high-risk patients, with extended duration commonly defined as 4 weeks post-operative prophylaxis. These findings have resulted in revised guidelines from organizations such as the American College of Chest Physicians (ACCP), the National Institute for Health and Care Excellence (NICE), and the American Society of Colon and Rectal Surgeons (ASCRS). Guidelines now advocate for extended duration of VTE in high-risk patients undergoing abdominal or pelvic surgery who are not at increased risk of bleeding [5, 6]. Enoxaparin, low-molecular-weight heparin, is the most common and the most studied medication of choice for extended prophylaxis. However, it requires daily (or ideally twice daily) injections [4, 5]. Compliance with enoxaparin, which ideally requires twice daily injections, has been shown to be near 60% in colorectal and gynecologic oncology patients, with

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Tab. I. Patient demographics and comorbidities.

	GROUP 1 (N = 72)
Age	62.4 (12)
Female	31 (61)
BMI	28.4 (5.5)
Weight loss	32 (63)
CAD	40 (78.4)
CHF	38 (74.5)
CCI	2 [1–3]
ASA	2 (75)
Indications for surgery	
Cancer	46 (90)
Diverticulitis	3 (5.9)
Other	2 (3.1)
Risk stratification of VTE (Caprini score)	
Moderate 0.7%	1 (1.96)
High 1.8%	6 (11.76)
High 4.0%	11 (21.57)
Highest 10.7%	33 (64.71)

BMI – Body Mass Index, CAD – Coronary Artery Disease, CHF – Congestive Heart Failure, CCI – Charslon Comorbidity Index, ASA – American Society of Anesthesiologists classification, VTE – Venous thromboembolism

Tab. II. Surgery performed and post-operative complications.

	N, (%)
Abdominal surgery	36 (71)
Pelvic surgery	15 (29)
Laparoscopic approach	30 (58.8)
Anastomotic leak	2 (3.9)
Superficial wound infection	7 (13.7)
Return to operating room	3 (5.9)
Major bleeding	1 (1.9)
Minor bleeding	2 (3.9)

patients preferring the tablet form of prophylaxis [7, 8].

Rivaroxaban is a factor Xa inhibitor approved for treatment of VTE and prophylaxis after orthopedic surgery [9, 10]. The daily oral administration may facilitate adherence. A number of studies comparing enoxaparin to rivaroxaban after orthopedic surgery and one study in trauma patients showed an equivalent safety and efficacy profile [2, 11–13]. However, the safety of rivaroxaban in extended prophylaxis after elective colon and rectal surgery has not been examined. The purpose of this study is to evaluate real world implementation and the safety of rivaroxaban for extended prophylaxis after major abdominal and pelvic surgery.

MATERIALS AND METHODS

Study design and population

This is a retrospective review of patients undergoing major colorectal surgery at a regional hospital in Kiev, Ukraine between 09/14/19 and 03/26/20. All patients undergoing abdominal surgery received peri-operative VTE prophylaxis with subcutaneous heparin and then transitioned to rivaroxaban once started on regular diet and assessed by the surgeon. During an early part of the study period in Ukraine, the generally recommended prophylactic dose of 10 mg (based on use in orthopedic procedures) was not available, so 15 mg daily dose was used. Later in the study, as more dosing became available, patients were switched to 10 mg per day dosing. Adjustments were made for decreased renal function as appropriate. Postoperatively, patients stayed on rivaroxaban for a total of at least 30 days (individual patient packs are available in 42 tablet quantities). Patients who received anticoagulation for other indications or refused post-discharge prophylaxis were excluded from the study.

Data

Patient demographics, indication for surgery, type of procedure, surgical approach, comorbidities and post-operative complications including major or minor bleeding, readmission, blood transfusion, and need for re-intervention were noted.

Outcomes

VTE was defined as a DVT diagnosed by Doppler ultrasound and /or computed tomography. Patient were examined daily while in the hospital and had screening for any potential signs of VTE including leg swelling, calf tenderness, SOB, drop in oxygen saturation. If suspicious signs were noted, further radiologic studies were ordered. If radiologic studies were ordered for different reason (CT scan for example), they were evaluated for the presence of portal vein thrombosis.

In addition, all patients were seen in a clinical setting within a month of surgery and evaluated. Major bleeding was defined based on ISTH (International Society of Thrombosis and Hemostasis guidelines and was defined as: fatal bleeding, bleeding that is symptomatic and occurs in a critical area or organ [14] and/or extra-surgical site bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 h to the bleeding and /or surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular) or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection, and/or surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. Patients' charts were reviewed and patients were surveyed to identify bleeding.

Tab. III. Patient survey results.

	N, (%)
Survey response rate	51 (100)
Completed 30-day course	50 (98)
Found rivaroxaban easy to use approach	51 (100)
Preferred oral route of prophylaxis (compared to injection)	51 (100)

This study was approved by the Institutional Review Board. Use of this medication including risks, benefits and reported side effects as well as current absence of indication in colorectal surgery was discussed with each patient. Only patients who gave consent to participate were included in the study. Patient risk for developing VTE was assessed using the Caprini score [15] (Tab. I.).

Phone survey

Scripted phone surveys were administered on post-operative day 30 to assess patients' compliance and satisfaction with the regimen. Contact was attempted 3 times via telephone by the treatment team. Surveys included questions assessing completion of the medication course, proportion of the tablets taken (in quartiles) if the course was not completed, and reasons for which the course was not completed. Commonly reported complications of rivaroxaban including bleeding, bruising, abdominal pain and dizziness as well as patient's preference for post-discharge prophylaxis were also ascertained.

Statistical analysis

Continuous data was described using means and standard deviations or median and interquartile range depending on normality. StataCorp. 2018. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC was used to complete all statistical analyses.

RESULTS

Demographics and comorbidities

A total of 51 patients were included in the study with an average age of 62.4 years. Cancer was the most common indication for surgery in 46 (90%) patients. A substantial proportion of patients had a pre-operative diagnosis of coronary artery disease (CAD) (40 patients, 78%) and congestive heart failure (CHF) (8 patients, 74.5%). Most had ASA II (75%) and a Charles Comorbidity index of 2. Thirty-two (63%) patients reported weight loss before surgery, although median pre-operative albumin was within normal range at 3.4 [3, 2–3, 8] (Tab. I.).

Operative details

Thirty-six (71%) and 15 (29%) patients underwent abdominal and pelvic surgeries, respectively. Procedures included low anterior resection (13), abdominoperineal resection (2), sigmoid/left colectomy (20), right colectomy (6), colostomy (6), total abdominal colectomy (1), transverse colectomy (2) and colostomy takedown (1). A laparoscopic approach was used in 30 patients (58.8%) (Tab. II.).

Post-operative outcomes

The average length of stay was 5 days (range 3–10 days) with an average of 2 days before passing flatus. Two patients (3.9%) developed an anastomotic leak requiring a return to the operating room for a washout and proximal diversion. An additional patient was taken to the operating room for a washout associated with bleeding (see below), bringing the total return rate to operating room to 5.9%. Seven patients (13.7%) developed superficial wound infections. There were no deaths during the study period (Tab. II.).

VTE prophylaxis and bleeding complications

The majority of patients (40 patients or 78.4%) received pre-operative subcutaneous heparin prophylaxis. All patients received post-operative subcutaneous heparin and transitioned to rivaroxaban when tolerating regular diet and had stable hemoglobin (all by POD #3). Patients were required to walk starting on POD #1. Patients were sent home on 30 days of rivaroxaban, dosed as closely as possible to their ideal weight-based calculation. All patients were assessed daily once in the hospital for signs suspicious for VTE such as leg swelling, calf tenderness, shortness of breath or drop in oxygen saturation. In addition, patients were again assessed in person when they returned for post-operative visit and all by POD #30. No VTE complications were noted during the post-operative period. Three patients developed bleeding complications. One patient developed intraluminal bleeding before initiation of rivaroxaban and was treated conservatively. One patient reported a subcutaneous hematoma during the post-operative phone survey. One patient was re-admitted with abdominal bleeding requiring a return to the operating room for a washout; the patient in this incident reported taking twice the prescribed dose of rivaroxaban. A total of 4 (7.8%) patients required blood transfusions, but all blood transfusions were done pre-operatively due to low hemoglobin on presentation and none were done for bleeding related complications.

Patient survey result

A phone survey was administered on post-operative day 30 with a 100% response rate. Fifty of 51 patients (98%) finished their full 30-day course of rivaroxaban (Tab. III.). A course was stopped early in the patient discussed above who took twice the recommended dose and was readmitted with abdominal bleeding. In addition, one patient noted a subcutaneous hematoma that self-resolved while on medication. Ninety-six percent of patients did not experience any side effects from rivaroxaban. All of the patients surveyed found this anticoagulation approach easy to use. When asked about their preferred method of anticoagulation, 100% of patients preferred the oral route compared to injections (using in-patient administration of heparin was the point of comparison).

DISCUSSION

This study demonstrates that the implementation of long-term post-operative prophylaxis with rivaroxaban after colon and rectal surgery is easy and safe. The oral course is preferred by patients and may be an acceptable alternative to the current standard, especially in a low resource environment.

Chemoprophylaxis remains the mainstay of VTE prevention in surgical patients [5]. Extended prophylaxis in high risk patients including cancer and inflammatory disease patients and patients undergoing high risk surgery has been recommended [2, 5]. Multiple studies showed this approach to decrease rates of VTE without a significant increase in rates of bleeding-related complications. Enoxaparin, a low-molecular-weight heparin has been a gold standard for extended VTE prophylaxis given its superior efficacy to unfractionated heparin as well as once a day prophylactic dosing [5, 6, 16]. However, compliance with these prophylactic recommendations remains an issue due to a combination of poor provider and patient compliance [7, 17]. In addition, cost and availability may limit access especially in low resource environments. Rivaroxaban, administered orally, has indications for treatment of VTE as well as prophylaxis in elective orthopedic surgery [10, 11]. A number of prospective trials evaluating rivaroxaban compared to enoxaparin showed improved outcomes for rivaroxaban. For example, Erikson et al. (RECORD trial) reported lower rates of major VTE in patients on rivaroxaban (0.2%) when compared to enoxaparin (2%, $p < 0.001$) without a significant increase in major bleeding (0.3 vs. 0.1% respectively, $p = 0.18$) [18]. Evaluation of rivaroxaban in a non-orthopedic population has been limited, however the existing data suggests that it may be similarly safe and effective. Kingdon et al. reported similar rates of VTE between rivaroxaban and enoxaparin in the adult trauma population (1.3% in both groups, $p = 1$) without a significant difference in post-operative bleeding complications [12].

In this study, there was one minor (hematoma in the outpatient setting) and one major bleeding complication that were attributed to this medication. The patient with major intra-abdominal bleeding required re-exploration and washout. The patient, however, admitted to having taken double the recommended dose in order to "improve prophylaxis". There were no other significant side effects that could be associated with rivaroxaban use. There were no clinically significant episodes of VTE in our study, but it was not powered to detect these complications.

The survey administered to patients showed that they preferred an oral route of prophylaxis compared to injections (all received subcutaneous heparin in the hospital and thus could compare). This was also possibly responsible for a much larger proportion of patients completing the full or near full course of prophylaxis than has been reported in literature. There was potentially a cultural component of the unusually high response to the survey since patients in Ukraine expect a portion of their post-surgical follow-up to be done via telemedicine, and thus anticipate and are willing to have phone conversations with providers.

This is the first study to our knowledge that evaluates real world use of rivaroxaban for extended prophylaxis after colorectal surgery that also includes a patient survey. At the time of this study, the cost of the course (42 days based on packaging) was $33–70 in Ukraine and was more affordable for patients when compared to enoxaparin ($100–150 for a 30-day course). In addition, injections require teaching and assistance. Both of the above may make rivaroxaban a suitable alternative to the current recommended extended prophylaxis within both rich and low resource environments. Other advantages of our study include high compliance with medication use and follow-up surveys. All patients included would be considered high risk and qualify for extended prophylaxis. A randomized, double-blind study, PROLPAS II has recently been initiated to further evaluate the role of rivaroxaban in extended prophylaxis after laparoscopic colorectal surgery.

This study has a number of limitations. A small number of patients included may underestimate the incidences of complications, both bleeding and VTE. Routine screening for post-operative VTE was not done due to regional limitation which can underestimate the true number of events, even if they were asymptomatic. The non-randomized nature of the trial may introduce bias. Although there was great compliance with the phone survey, recall bias may be an issue. Due to packaging limitations, patients were given 42 total days of rivaroxaban, which is longer than the standard 30-day prophylaxis. Patients were instructed to stop taking the medication after finishing the 30-day course, although it is possible that some patients took it longer and potential issues associated with that were not accounted for in this study. For most of the study duration, only 2 dosages were available and both were higher than the 10 mg per day dose currently used for prophylaxis after orthopedic surgery.

CONCLUSION

The implementation of extended prophylaxis with rivaroxaban is easy, safe and does not increase rates of post-operative bleeding. This prophylactic approach is preferred by patients and has good patient compliance. Larger studies that assess the efficacy of rivaroxaban for VTE prophylaxis and studies comparing patient tolerance of oral versus subcutaneous formulations are needed.

REFERENCES

1. Kourlaba G., Relakis J., Mylonas C. et al.: The humanistic and economic burden of venous thromboembolism in cancer patients: a systematic review. Blood Coagul Fibrinolysis., 2015; 26(1): 13–31.
2. Gould M.K., Garcia D.A., Wren S.M. et al.: Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest., 2012; 141(2 Suppl): e227S–e277S.
3. Agnelli G., Bolis G., Capussotti L. et al.: A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg., 2006; 243(1): 89–95.
4. Alhassan N., Trepanier M., Sabapathy C. et al.: Risk factors for post-discharge venous thromboembolism in patients undergoing colorectal resection: a NSQIP analysis. Tech Coloproctol., 2018; 22(12): 955–964.
5. Fleming F., Gaertner W., Ternent C.A. et al.: The American Society of Colon and Rectal Surgeons Clinical Practice Guideline for the Prevention of Venous Thromboembolic Disease in Colorectal Surgery. Dis Colon Rectum., 2018; 61(1): 14–20.
6. Lieberman J.R.: American College of Chest Physicians evidence-based guidelines for venous thromboembolic prophylaxis: the guideline wars are over. J Am Acad Orthop Surg., 2012; 20(6): 333–335.
7. Marchocki Z., Norris L., O'Toole S., Gleeson N., Saadeh F.A.: Patients' experience and compliance with extended low molecular weight heparin prophylaxis post-surgery for gynecological cancer: a prospective observational study. Int J Gynecol Cancer., 2019.
8. Peidro-Garces L., Otero-Fernandez R., Lozano-Lizarraga L.: Adherence to and satisfaction with oral outpatient thromboembolism prophylaxis compared to parenteral: SALTO study. Rev Esp Cir Ortop Traumatol., 2013; 57(1): 53–60.

9. Bala A., Huddleston J.I., Goodman S.B., Maloney W.J., Amanatullah D.F.: Venous Thromboembolism Prophylaxis After TKA: Aspirin, Warfarin, Enoxaparin, or Factor Xa Inhibitors? Clin Orthop Relat Res., 2017; 475(9): 2205–2213.
10. 10. Cohoon K.P., De Sanctis Y., Haskell L., McBane R.D., Spiro T.E.: Rivaroxaban for thromboprophylaxis among patients recently hospitalized for acute infectious diseases: a subgroup analysis of the MAGELLAN study. J Thromb Haemost., 2018; 16(7): 1278–1287.
11. Karampinas P.K., Megaloikonomos P.D., Lampropoulou-Adamidou K. et al.: Similar thromboprophylaxis with rivaroxaban and low molecular weight heparin but fewer hemorrhagic complications with combined intra-articular and intravenous tranexamic acid in total knee arthroplasty. Eur J Orthop Surg Traumatol., 2019; 29(2): 455–460.
12. Kingdon L.K., Miller E.M., Savage S.A.: The Utility of Rivaroxaban as Primary Venous Thromboprophylaxis in an Adult Trauma Population. J Surg Res., 2019; 244: 509–515.
13. Yu Z., Shan P., Yang X., Lou X.J.: Comparison of efficiency and safety of rivaroxaban, apixaban and enoxaparin for thromboprophylaxis after arthroplastic surgery: a meta-analysis. Biosci Rep., 2018; 38(6): BSR20180423.
14. Schulman S., Kearon C.: Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost, 2005; 3(4): 692–694; doi: 10.1111/j.1538-7836.2005.01204.x. PMID 15842354.
15. Bahl V., Hu H.M., Henke P.K., Wakefield T.W., Campbell D.A. et al.: A validation study of a retrospective venous thromboembolism risk scoring method. Ann Surg., 2010; 251(2): 344–350.
16. Geerts W.H., Jay R.M., Code K.I. et al.: A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med., 1996; 335(10): 701–707.
17. Merkow R.P., Bilimoria K.Y., Sohn M.W. et al.: Adherence with postdischarge venous thromboembolism chemoprophylaxis recommendations after colorectal cancer surgery among elderly Medicare beneficiaries. Ann Surg., 2014; 260(1): 103–108.
18. Eriksson B.I., Borris L.C., Friedman R.J. et al.: Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med., 2008; 358(26): 2765–2775.
19. Becattini C., Pace U., Rondelli F. et al.: Rivaroxaban for Extended Antithrombotic Prophylaxis After Laparoscopic Surgery for Colorectal Cancer. Design of the PRO-LAPS II STUDY. Eur J Intern Med., 2020; 72: 53–59.

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