

One Size Does Not Fit All: Venous Thromboembolism Prophylaxis in Colorectal Cancer

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ABSTRACT

Background and Objectives: Venous thromboembolisms (VTEs) in patients who have undergone a colorectal cancer operation increases morbidity and mortality, lengthens recovery time, and are costly. The current common standard is a 28-day prophylactic regimen of 40 mg enoxaparin daily. This study aims to examine the variability in prophylaxis discharge prescriptions at one institution, report 30-day postoperative incidence of venous thromboembolisms and bleeding, and to offer a new protocol for VTE prophylaxis in postoperative patients.

Methods: This retrospective case series occurred at Abington-Jefferson Health Hospital in Abington, PA. The electronic medical record was searched for patients who underwent an operation for colorectal cancer from October 2019 to mid-March 2020 and all discharge prophylaxis regimens were recorded and patient demographics were analyzed. Outcomes were measured by rate of VTEs and postoperative complications such as bleeding, transfusions, re-admission, and intensive care admission in the 30-day postoperative period.

Results: Eighteen of 57 patients received a medication besides 40 mg of enoxaparin daily. These 18 patients were divided into six different sub-groups of various prophylaxis regimens. No patients developed a venous thromboembolism. Four of 18 patients experienced postoperative bleeding complications.

Conclusions: Patients with similar pre-operative comorbidities have various venous thromboembolism perioperative prophylaxis regimens prescribed. Despite prescription variations, VTE rates remain negligible. Patients with different comorbid conditions may require alterations to the traditionally prescribed 40 mg enoxaparin daily. Upon discharge, aspirin 81 mg with 40 mg of enoxaparin daily for high-risk patients shows benefits, but requires further investigation.

Key Words: Colorectal cancer, Enoxaparin, Venous thromboembolism prophylaxis.

INTRODUCTION

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are postoperative complications in colorectal cancer patients, with the literature citing a DVT rate of 2.6 to 2.8%. The effects of venous thromboembolisms (VTEs) range from uncomplicated postoperative morbidities such as increased length of hospital stay to death. The estimated health care system costs are between \$31,2170 to \$38,296 per patient. One study found that colorectal patients have a 10% greater chance of developing a DVT than general surgical patients. The increased risk in colorectal patients is thought to be due to pelvic dissections, patient positioning, and common patient cohort characteristics; specifically pre-existing inflammation due to malignancy or inflammatory bowel disease.¹

The American Society of Colon and Rectal Surgeons (ASCRS) recommends extended-duration pharmacological thromboprophylaxis in patients undergoing colorectal cancer resection.¹ Forty mg enoxaparin daily is most commonly prescribed. However, this is not standard across all colorectal practices, and for patients with different comorbidities and body mass profiles, may not be sufficient. In fact, within our single institution, on a single surgical service, there remains discrepancy in the type of VTE prophylaxis prescribed for patients by attending colorectal surgeons. The aim of this case series is to examine the variability in VTE prophylaxis prescriptions at one institution, report 30-day postoperative incidence of VTE and

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Table 1.
Complications Rates for Non-Standard Dose Venous Thromboembolism Prophylaxis

Subgroup: VTE Rx	Total Number of Patients	M:F	Average Age (years)	Complication Rate	VTE Rate
1: enoxaparin 60 mg bid	1	1:0	58	0	0
2: apixaban 5 mg	1	1:0	75	0	0
3: warfarin	4	3:1	86	0	0
4: enoxaparin 40 mg / ASA 81	6	4:2	71	2:6	0
5: enoxaparin 30 mg bid	3	2:1	70	1:3	0
6: rivaroxaban	3	2:1	63	1:3	0

VTE, venous thromboembolism; Rx, prescription; M, male; F, female.

bleeding in colorectal cancer patients receiving regimens of extended-duration thromboprophylaxis other than 40 mg enoxaparin daily, and to suggest a new protocol for VTE prophylaxis prescriptions at discharge.

MATERIALS AND METHODS

We used the electronic medical record (EMR) to identify patients who had an oncological colorectal operation by a colorectal attending from October 2019 to early March 2020 at Abington-Jefferson Health Hospital (Abington, PA). All patients were discharged on VTE prophylaxis. Eighteen out of 53 patients underwent an operation and were discharged on VTE prophylaxis other than 40 mg enoxaparin. The remaining 35 of 53 patients were discharged on 40 mg enoxaparin daily. These medications were prescribed by residents or advanced practice practitioners after receiving confirmation from the colorectal attending surgeon prior to discharge. The regimens included home anticoagulation resumption, 40 mg enoxa-

parin daily, 30 mg enoxaparin two times a day (bid), or 40 mg enoxaparin daily and aspirin (ASA) 81 mg.

Patient demographics and comorbid conditions, type of surgery, in-house VTE prophylaxis prescription, discharge VTE prophylaxis prescription, complication rate and type, readmission cause, length of stay on the surgical floor and intensive care unit, need for blood transfusion, transfusion hemoglobin, starting and peak creatinine, smoking history, and disposition destination were obtained from the EMR. Data were tabulated and analyzed with Microsoft Excel.

RESULTS

A search of the Abington-Jefferson Health Hospital EMR identified 53 patients who underwent a colorectal cancer operation by our colorectal surgeons between October 2019 and mid-March 2020 (**Table 1, Table 2, Table 3**). Eighteen of those 53 patients were discharged on VTE

Table 2.
Patient Comorbidities by Venous Thromboembolism Prophylaxis Type

	40 mg Lovenox n = 35 (%)	Other VTE ppx n = 18 (%)	P-Value
Atrial fibrillation	3 (8.6)	7 (38.9)	< 0.05
Diabetes mellitus	4 (11.4)	1 (5.6)	NS
Hyperlipidemia	9 (25.7)	13 (72.2)	< 0.05
Hypertension	16 (45.7)	16 (88.9)	< 0.05
Coronary artery disease	0 (0)	6 (33.3)	< 0.05

NS, not significant; < 0.05 = significant.

VTE, venous thromboembolism; ppx, prophylaxis.

Table 3.
Indications and Demographics for Lovenox 40 mg Venous Thromboembolism Prophylaxis

Patient	Cancer Type	Colectomy Type	Readmission or Complication	Sex	BMI	Age	LOS	ICU LOS	Transfusion Required	Bleeding Requiring Intervention
1	R colon	open R	Y	F	27.3	78	7	0	Y	N
2	L colon	laparoscopic L	Y	F	23.3	65	11	0	N	N
3	Rectal	transanal total mesorectal	Y	M	28.2	68	10	0	N	N
4	R colon	laparoscopic R	N	F	22.6	37	2	0	N	N
5	L colon	laparoscopic L	N	M	39.9	50	2	0	N	N
6	L colon	laparoscopic L	N	F	31.3	79	3	0	N	N
7	R colon	laparoscopic R	N	F	23.7	63	2	0	N	N
8	R colon	laparoscopic R	N	F	22.4	57	3	0	N	N
9	R colon	open R	N	F	22.6	73	8	0	N	N
10	Rectal	laparoscopic low anterior	Y	M	30.9	66	5	0	N	N
11	Rectal	open low anterior	Y	F	26.7	69	4	0	N	N
12	R colon	laparoscopic R	Y	F	33.7	45	31	5	Y	Y
13	R colon	laparoscopic R	N	F	19.8	80	3	0	N	N
14	R colon	open R	N	M	25.4	68	2	0	N	N
15	Rectal	open loop colostomy	N	M	23.6	59	3	0	N	N
16	R colon	laparoscopic R	N	F	26.6	91	33	0	Y	N
17	R colon	laparoscopic R	N	F	36.6	51	3	0	N	N
18	R colon	laparoscopic R	N	M	25.3	70	3	0	N	N
19	Rectal	laparoscopic low anterior	N	F	39.4	52	3	0	N	N
20	Rectal	robotic abdominoperineal	Y	F	31	71	5	0	Y	N
21	Rectal	laparoscopic low anterior	N	M	34.8	40	8	0	N	N
22	R colon	laparoscopic R	N	M	19.2	37	9	0	N	N
23	L colon	laparoscopic L	N	F	22.3	52	3	0	N	N
24	Rectal	laparoscopic low anterior	N	F	22	69	9	0	N	N
25	Rectal	laparoscopic low anterior	N	F	32.2	95	5	0	N	N
26	Rectal	robotic low anterior	N	F	23.2	83	5	0	Y	N
27	R colon	laparoscopic R	N	M	26.4	83	3	0	N	N
28	Rectal	laparoscopic low anterior	N	M	32.9	51	3	0	N	N
29	L colon	laparoscopic L colectomy	N	F	41.1	39	3	0	N	N

Table 3.
Continued

Patient	Cancer Type	Colectomy Type	Readmission or Complication	Sex	BMI	Age	LOS	ICU LOS	Transfusion Required	Bleeding Requiring Intervention
30	Rectal	laparoscopic low anterior	N	M	30.3	60	8	0	N	N
31	L colon	open loop colostomy	N	F	18.4	74	7	0	N	N
32	Rectal	laparoscopic low anterior	N	F	36	55	3	0	Y	N
33	R colon	laparoscopic R	N	M	27.1	68	6	0	N	N
34	L colon	laparoscopic L	N	M	30.6	48	3	0	N	N
35	R colon	laparoscopic R	N	F	28.3	68	3	0	N	N

BMI, body mass index; LOS, length of stay; ICU, intensive care unit; R, right; L, left; Y, yes; N, no.

prophylaxis other than 40 mg enoxaparin daily and divided into six subgroups based on the medications prescribed and potential complications that occurred. All patients with a diagnosis of rectal cancer received radiation therapy. Approximately 85% of the surgeries were minimally invasive, and almost all surgeries were performed electively (**Table 4**). These 18 patients are divided into subgroups below.

The first subgroup consisted of one patient who was discharged on 60 mg enoxaparin bid, the same dose received in-house. The patient was male, with a BMI of 52.2, and had no postoperative complications or need for readmission.

The second subgroup was composed of one patient who was discharged on his home dose of apixaban 5 mg and ASA 81 mg for a history of atrial fibrillation. During hospitalization he received a heparin infusion as a bridge prior to and after the operation. No in-house or postoperative complications were noted.

The third subgroup consisted of four patients, all with a history of atrial fibrillation, discharged on their presurgical dosage of warfarin. While inpatient, two patients in this cohort received 40 mg daily of enoxaparin, one received 30 mg enoxaparin daily, and one received 30 mg enoxaparin bid. None of these patients had postoperative complications.

The fourth subgroup contained six patients discharged on the standard 40 mg enoxaparin daily, in addition to resuming their home ASA 81 mg. In this subgroup, four of the six patients received solely 40 mg enoxaparin daily and no ASA while inpatient. One of these patients received a blood

transfusion for symptomatic anemia. The other two out of six patients received ASA 81 mg with 40 mg enoxaparin daily while inpatient and were discharged on this regimen. One of these two patients was upgraded to the intensive care unit (ICU) and received a blood transfusion for hypotension and acute blood loss anemia. After discharge, none of these six patients had any further issues.

The fifth subgroup was composed of three patients who were started in-house on 30 mg enoxaparin bid. Two of these three patients were discharged on that same dose. One of the three patients experienced postoperative symptomatic blood loss anemia and required transfusion and an interventional colonoscopy. He was discharged on 40 mg enoxaparin daily. None of the three patients experienced any further complications after discharge.

The sixth subgroup contained three patients who were discharged on rivaroxaban, a home medication taken pre-operatively for treatment of previously diagnosed DVT or atrial fibrillation. While inpatient, two of these three patients received 40 mg daily of enoxaparin and one received 5,000 units of heparin every eight hours. One of the three patients was readmitted to the ICU on postoperative day seven with rectal bleeding. In the ICU, hemoglobin remained stable and he did not receive any blood transfusions, but was given prothrombin complex concentrate on admission to reverse the effects of rivaroxaban.

No patients in any of the subgroups experienced VTEs during their 30-day postoperative period.

Out of the 35 of 53 patients who were prescribed only 40 mg enoxaparin daily for VTE prophylaxis, none of them

Table 4.
Indications and Demographics for Non-Lovenox 40 mg Venous Thromboembolism Prophylaxis

Patient	Cancer Location	Colectomy Type	Readmission or Complication	Sex	BMI	Age	LOS	ICU	Transfusion Required	Bleeding Requiring Intervention
1	L colon	laparoscopic L	N	F	29	77	4	0	N	N
2	Rectal	laparoscopic abdominoperineal	N	M	27.9	73	3	0	N	N
3	R colon	open L	N	M	34.3	58	4	0	Y	Y
4	Rectal	laparoscopic low anterior	N	F	23.1	80	4	0	N	N
5	L colon	open L	N	M	27	78	5	0	Y	N
6	Rectal	laparoscopic low anterior	N	M	29	63	4	0	N	N
7	Rectal	robotic low anterior	N	M	32	85	10	4	Y	N
8	Rectal	robotic low anterior	N	M	25.3	58	3	0	N	N
9	R colon	laparoscopic R	N	F	33.4	59	2	0	N	N
10	transverse colon	open transverse loop	N	M	52.2	58	4	0	N	N
11	Rectal	laparoscopic low anterior	Y	M	29.8	57	3	0	N	N
12	R colon	laparoscopic R	Y	M	34.2	68	2	0	N	N
13	L colon	open transverse loop	N	F	30.6	63	10	0	N	N
14	L colon	laparoscopic L	N	M	28.2	89	4	0	N	N
15	R colon	laparoscopic R	N	M	36.3	82	10	0	N	N
16	Rectal	laparoscopic low anterior	N	M	29.5	83	3	0	N	N
17	Rectal	transanal total mesorectal	N	F	33.2	90	2	0	N	N
18	R colon	laparoscopic R	N	M	37.4	75	13	0	N	N

BMI, body mass index; LOS, length of stay; ICU, intensive care unit; R, right; L, left; Y, yes; N, no.

developed VTEs during their 30-day postoperative period (**Table 3**). Seven of the 35 patients had to be readmitted during the 30-day postoperative period, but for reasons other than bleeding or anti-VTE medication complications. Six of the 35 patients had to receive transfusions while in-house. Two of the 35 patients were switched from 40 mg daily of Lovenox to no VTE prophylaxis medication on discharge.

DISCUSSION

Currently, at Abington-Jefferson Health Hospital there is a protocol for prescribing VTE prophylaxis upon discharge

for postoperative colorectal cancer patients, which follows the ASCRS guidelines that recommend 28 days of postsurgical VTE prophylaxis.² Forty mg enoxaparin daily is most commonly prescribed for the average patient. However, for patients with pre-operative anticoagulation or antiplatelet requirements, increased risk of VTEs, and a greater BMI, the dose and type of VTE prophylaxis medication is left to the attending surgeon's discretion.

All colorectal attending surgeons at this institution follow the current protocol and agree upon prescribing VTE prophylaxis for the extended duration of 28 days. However, as highlighted by the six subgroups in this case

series, even in a controlled environment at single institution, on a single surgical service, with standardized workflow between residents, advanced practice practitioners, and attending surgeons, there remains a large variability in post-discharge medication reconciliation for VTE prophylaxis. The reason for this variability is unclear, but is thought mainly to be due to the colorectal attending's preference. This trend was initially observed and was a motivation to perform our study. After review, it is thought that implementing a protocol for routine postoperative colon cancer resections will reconcile this difference, as (**Chart 1**) reflects. We hope to analyze postimplementation data to understand the effects of this change.

VTE rates at our institution after colon cancer surgery are extremely low. This suggests that a more liberal variability for patient discharge VTE prophylaxis regimens should be accepted. However, these low rates did not come without complications. Four of the 18 cases reported did have 30-day postoperative complications that led to either a blood transfusion, ICU admission, intervention for bleeding, and/or readmission.

Based on the findings in this case series and our research, we have developed a new protocol in order to standardize how patients with different comorbidity profiles are treated for VTE prophylaxis after discharge (**Chart 1**). Not only will this provide better consistency with VTE prophylaxis prescriptions for high risk patients, but it also serves as a mechanism to combat the inherent error presented by patient handoffs and resident team shiftwork. The new protocol and the reasoning for our decisions are described in the following paragraphs.

Our new protocol suggests that patients who are already taking anticoagulation medication prior to surgery should

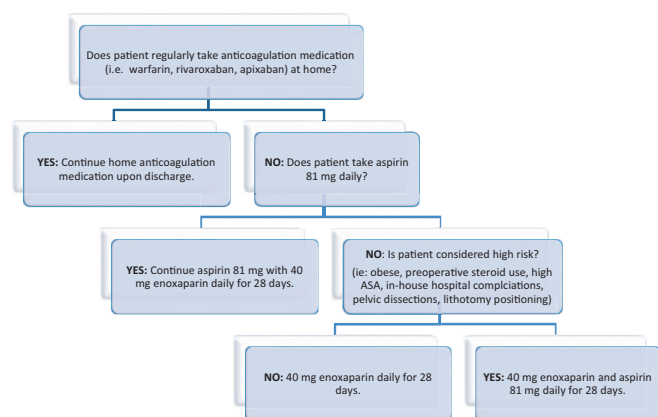


Chart 1: New proposed VTE prophylaxis prescription protocol for postoperative colorectal cancer patients.

resume their home medication upon discharge. Those patients taking ASA 81 mg daily prior to surgery are to resume this medication upon discharge, in addition to 40 mg enoxaparin daily for 28 days. For patients who are not anticoagulated or taking ASA 81 mg prior to surgery there are two options. Low risk patients should be discharged on 40 mg enoxaparin daily for 28 days. Patients deemed to be high risk will be discharged on 40 mg enoxaparin daily with ASA 81 mg for 28 days. Patients at increased risk for VTE development are defined as those who are obese, have pre-operative steroid use, a high American Society of Anesthesia class, pre-discharge complications, pelvic dissections, prolonged surgeries (greater than three hours), lithotomy positioning, and/or preexisting inflammatory states and malignancy.¹

Recent studies have shown that the anti-Xa levels in patients taking enoxaparin 40 mg daily are below expected for VTE prophylaxis. Therefore, it was proposed that extending coverage with a twice per day model of VTE prophylaxis administration could reduce VTE rates and increase anti-Xa levels. Thirty mg enoxaparin bid is commonly prescribed by orthopedic surgeons for postoperative hip or knee replacement patients to prevent VTEs. Despite the increased frequency of enoxaparin administration, one recent study showed that the therapeutic anti-Xa level is actually reduced, compared to those patients who received 40 mg enoxaparin daily. At our institution, it is not standard to obtain routine anti-Xa factor levels on patients prescribed enoxaparin; therefore, the therapeutic efficacy of VTE prophylaxis is unknown.³ Of the three patients that received 30 mg bid in this case series, none developed a VTE during the 30-day postoperative period. Yet, one out of three patients in this subgroup, did require transfusion and interventional colonoscopy for postoperative bleeding. This suggests that while an increased frequency of enoxaparin administration leads to similar outcomes of reduced VTE rates as described in patients with standard regimens, it still likely does not lead to adequate anti-Xa levels for VTE prophylaxis, and is not without morbidity. Further studies with a larger sample set are needed to resolve this discrepancy.

Eight of the 18 patients in this case series resumed their home therapeutic anticoagulation upon discharge. The majority of these patients were taking anticoagulation for a prior diagnosis of atrial fibrillation or a previously diagnosed DVT. Upon discharge, patients resumed their home doses of rivaroxaban, warfarin, or apixaban. Of these eight patients, none developed VTE complications in the 30-day postoperative period. However, one patient was

readmitted to the ICU for rectal bleeding on postoperative day seven, for which he underwent an interventional colonoscopy, but did not receive any blood transfusions. Since these patients were already prescribed anticoagulation doses that were more potent than VTE prophylactic doses, their home medications provided excellent prophylaxis against VTEs. Yet, continuing these medications does come with risks. As described in the literature, hemorrhagic complications outnumbered thromboembolic complications three-fold in patients that were anticoagulated and undergoing colorectal or abdominal wall surgery. This trend was paralleled in our study as well. Therefore, patients who are already anticoagulated should be considered “high risk” and monitored closely for bleeding complications in the postoperative period.⁴

Six patients in this case series were prescribed both enoxaparin 40 mg daily and ASA 81 mg upon discharge. None developed VTEs during the 30-day postoperative period. One experienced symptomatic acute blood loss anemia postoperatively, while taking the combined regimen as an inpatient. Zero patients were readmitted after discharge for any complications, including bleeding. Previous studies have found ASA 81 mg to be effective prophylaxis against VTEs.⁵ Although further investigation would need to be undertaken, this case series suggests that a VTE prophylaxis regimen inclusive of ASA 81 mg upon discharge could be more beneficial than 40 mg enoxaparin alone or 30 mg enoxaparin bid, for patients deemed to be at high-risk for VTE development. In the orthopedic surgery literature, there has been ongoing research about patients undergoing total hip arthroplasty or total knee arthroplasty taking both aspirin and enoxaparin, and some orthopedic guidelines currently recommend this combined regimen.⁶

The limitations of this study are the fact that it is a retrospective case series at a single institution consisting of only 18 patients. Furthermore, we do not have the resources for obtaining anti-Xa levels, which could have helped to triage patients into a different VTE prophylaxis arm after surgery. Future studies assessing the safety and benefits of these VTE prophylaxis regimens will need to include a larger patient population and preferably take place as a randomized controlled trial.

CONCLUSIONS

VTEs in patients who have undergone an oncological colorectal operation increases morbidity and mortality, lengthens recovery time, and are costly. The current

standard calls for a 28-day post-discharge prophylactic regimen for which most surgeons use 40 mg enoxaparin daily.

Notwithstanding, patients with different comorbid conditions may require alterations in this medication regimen. As can be seen by the six subgroups presented in this case series, even with multidisciplinary patient care teams on a single surgical service at a single institution, patients with similar pre-operative comorbidities have different perioperative prophylaxis regimens prescribed. Despite these prescription variations, VTE rates remain negligible. Since there is no clear reason for this variability, we felt there was a need at our institution to develop a new VTE prophylaxis protocol that we plan to implement and trend outcomes for. Moreover, this case series also highlights the benefits and minimal risk of prescribing ASA 81 mg with 40 mg enoxaparin daily upon discharge for VTE prophylaxis in patients deemed high risk for VTEs. Further investigation is needed, but at this time, this regimen appears to be a viable option that potentially has greater benefits than solely enoxaparin 40 mg daily or enoxaparin 30 mg bid.

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