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Evaluation of practice of postoperative thromboembolism prophylaxis among colorectal cancer patients in the National Cancer Hospital

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ABSTRACT

The study was carried out to investigate the appropriateness of thromboprophylaxis for colorectal cancer patients after surgery. A descriptive retrospective study was conducted among patients aged 18 and above, who underwent colorectal cancer surgery at the Department of Internal Medicine, National Cancer Hospital from January 2021 to June 2021. Criteria for appropriate prophylaxis were set up based on the international and local thromboprophylaxis guidelines and anticoagulants' summary of product characteristics (SmPC). The prophylaxis regimen of patients after 166 surgeries were evaluated. The major surgeries accounted for 92.8 % of the surgeries. The proportions of patients with high and moderate risks of postoperative venous thromboembolism (VTE) were 91% and 8%, respectively. The rate of patients who received any form of thromboprophylaxis was 16.3% while the rate of patients indicated with appropriate methods of VTE prevention was 83.7%. The proportion of patients without prophylaxis was significantly higher among patients with moderate VTE risk compared to those at high risk (p=0.004). Among patients with appropriate thromboprophylaxis, 100% were prescribed an appropriate anticoagulant at a suitable dose. However, all of them initiated the therapy later than the recommendations and 96.4% had shorter prophylactic duration. There was still a gap in the appropriate practice of post-surgical thromboprophylaxis for patients undergoing colorectal cancer treatment. The initiation time and the duration of prevention still deviated from the standard recommendations.

Keywords: *colorectal cancer, venous thromboembolism (VTE), thromboprophylaxis*

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INTRODUCTION

Venous thromboembolism (VTE), which typically presents as deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third leading cause of cardiovascular-associated death (after stroke and myocardial infarction) [11]. Venous thromboembolism is a common

complication in patients undergoing surgery. Thromboprophylaxis provides the most effective means of reducing morbidity and mortality in these patients. More extended use of prophylaxis, besides the early mobilization and improved perioperative care, has been demonstrated to reduce the risk of VTE in surgical patients.

Cancer is a primary risk factor for VTE [8]. Cancer patients have a 4-7 fold increased risk of venous thrombosis compared with the general population or patients without cancer, the risk of venous thrombosis depends on the pathophysiology of cancer, characteristics of the patient, and treatment, with increased risk in surgical patients. Individuals with cancer are at risk for thrombotic complications and death after thromboembolism, and may also have a higher risk of bleeding with anticoagulation administration [9]. Therefore, making decisions about the use of prophylactic anticoagulants is more challenging, requiring careful consideration of the relative risks and benefits.

The efficacy and safety of VTE prevention in cancer patients have been shown in clinical trials, especially in cancer surgery patients. Several clinical trials have been conducted exclusively in patients undergoing surgery for colorectal cancer. Based on sufficient evidence, current guidelines unanimously recommend extended prophylaxis with anticoagulation for up to 4 weeks for surgical patients with abdominal and pelvic cancer, including colorectal cancer [6,9,10,12,14]. However, a study in the US showed that only 13% of colorectal cancer patients were prescribed long-term anticoagulation after surgery. Although extended-duration thromboprophylaxis for patients tended to increase gradually over time, it has not changed significantly and appeared differently among facilities [13]. In Vietnam, thromboprophylaxis among cancer patients has not been studied yet. Therefore, this study aimed to examine the appropriateness of thromboprophylaxis among colorectal cancer patients after surgery in a national cancer hospital in Vietnam.

MATERIALS AND METHODS

Design and patients

A descriptive study was conducted at the Vietnam National Cancer Hospital to evaluate the appropriateness of VTE prophylaxis for colorectal cancer patients after surgery. Patients aged 18 or older and underwent colorectal cancer surgery at the hospital from January 2021 to June 2021 were eligible for inclusion. Those who used anticoagulants before surgery were excluded. Data on patients' characteristics, surgery, and thromboprophylaxis was retrospectively retrieved from medical records.

The study subjects were classified as having a moderate or high risk of VTE based on the CAPRINI score [5]. They were considered to have a risk of bleeding complications if they had at least one of the following factors: active bleeding, previous major bleeding, known and untreated bleeding disorder, severe renal or hepatic failure, thrombocytopenia, acute stroke, uncontrolled systemic hypertension, lumbar puncture, epidural, or spinal anesthesia within the previous 4 hours or the next 12 hours [4,6]. Those with severe renal or hepatic failure, brain hemorrhage, active bleeding, history of thrombocytopenia, especially heparin-induced thrombocytopenia (HIT), allergy to anticoagulants, congenital or acquired coagulopathy, lumbar puncture, taking antiplatelet drugs, less than 100,000/mcL of platelets, cranial surgery, spinal cord surgery, or intraocular hemorrhage were classified as having a contraindication to anticoagulants [8]. Major surgery was defined as any procedure performed under general anesthesia, anticipated duration of surgery longer than 45 minutes [15]. Those that did not meet the criteria for major surgery defined as were minor.

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Assessment of the appropriateness of VTE prophylaxis

The selection of method of prophylaxis, the indication, dosage, initiation time and duration of anticoagulants, were assessed to determine the appropriateness of thromboprophylaxis. Criteria for the appropriateness were set up based on the international guidelines such as American College of Chest Physicians (ACCP) 2016, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), the Vietnam Heart Association guideline about VTE prophylaxis, and the summary of product characteristics (SmPC) of the anticoagulants such as unfractionated heparin (UFH), dalteparin, enoxaparin [5,8,10,14].

The method of prophylaxis was considered appropriate if a mechanical or pharmacologic method was prescribed for patients with a moderate risk and a pharmacologic method was used for those with a high risk of VTE. Among patients with contra-indication to anticoagulants, a mechanical method was appropriate for both moderate and high-risk patients [5]. Otherwise, patients without prophylaxis or with a method that was different from the above recommendation were classified as inappropriate.

Among patients with appropriate pharmacologic methods, the choice of anticoagulant, drugs dose, initiation time, dose, and duration of prophylaxis was further evaluated. If patients were prescribed UFH, dalteparin, or enoxaparin, the indication of anticoagulants was considered appropriate [5,6,8,10,12,14]. However, dalteparin was not evaluated due to its unavailability at the study hospital. Appropriate doses of the anticoagulants were determined based on the SmPCs of the aforementioned anticoagulants and patients' condition, liver and kidney functions [17,18,19]. While the initiation of UFH 2 to 4 hours before surgery or between 6 to 24 hours after skin closure was appropriate, enoxaparin should be initiated between 10 to 12 hours preoperatively or between 12 to 24 hours after skin closure [6,14,16,17,18,19]. As for the duration, patients with major surgery and a high risk for VTE should be prescribed an anticoagulant for 28 ± 3 days, while others should use it for at least 7 days [6,8,10,12,14].

Statistical Analysis

Descriptive statistics were used to describe patient characteristics and clinical data. The median and interquartile range (IQR) were used for the continuous variables, and percentages and frequencies were used for categorical variables. Fisher exact test or Chi square was utilized for the comparison between groups and the level of significance was set at 0.05.

RESULTS

Characteristics of the study subjects

A total of 149 patients with 166 surgeries were included. The median age was 61 years. Males accounted for roughly 60% of patients, and nearly 88% had a BMI less than 25 kg/m^2. The major surgeries were 92.8%. The most common surgery was colorectal resection (78.9%). Most of the patients had a high risk of VTE (91.0%). While 90.4% of patients had a risk of bleeding, no one was contra-indicated to anticoagulants (Table 1).

Table 1: *Patient Characteristics*

Variables	n (%)
n = 149 patients	

Variables		n (%)
Age	Median (IQR)	61 (55-68)
Gender	Male	89 (59.7%)
	Female	60 (40.3)
BMI	< 25 kg/m^2	131 (87.9%)
	≥ 25 kg/m^2	18 (12.1%)
Cancer location	Colon	75 (50.3)
	Rectal	74 (49.7)
Pre-operation cancer stage	I- II	41 (27.5)
	III	74 (49.7)
	IV	23 (15.4)
	No information	11 (7.4)
n = 166 surgeries		
Surgical site	Colorectal resection	131 (78.9%)
	Others	35 (21.1%)
Type of surgery	Major	154 (92.8%)
	Minor	12 (7.2%)
Risk VTE	Moderate	15 (9.0%)
	High	151 (91.0%)
Anticoagulants contraindication	No	166 (100%)
	Yes	0 (0%)
Bleeding risk	No	16 (9.6%)
	Yes	150 (90.4%)

Appropriateness of thromboprophylaxis

Selection of prophylaxis methods

Of 166 surgeries, the rate of patients received any form of thromboprophylaxis was 16.3% while 83.7% of patient received appropriate methods of thromboprophylaxis. The selection of appropriate methods was seen in 86.8% of patients with high risk of VTE, which was significantly higher than that of patients with moderate risk (53.0%) (Figure. 1).

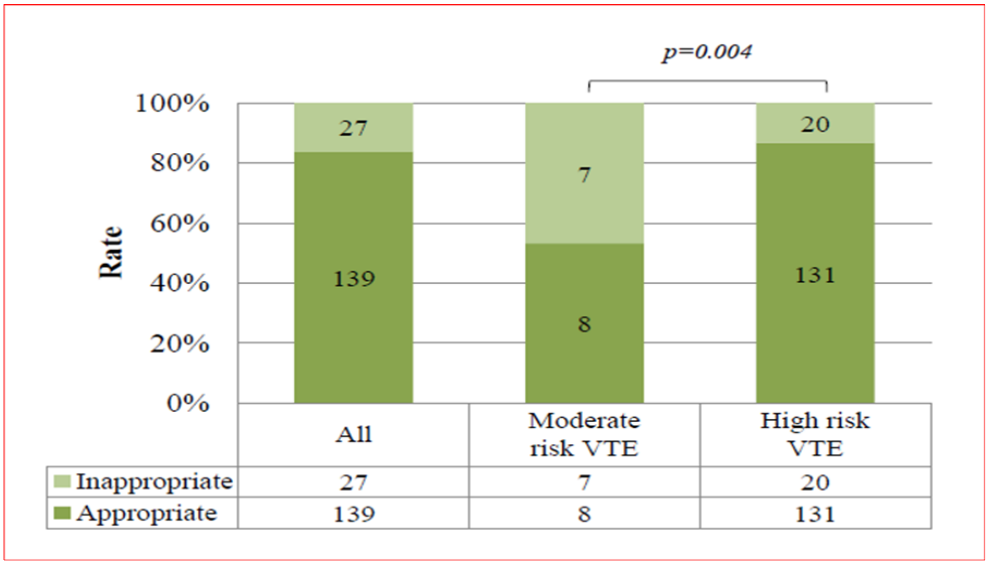

Figure 1: *Appropriateness of selection of thromboprophylaxis methods*

Anticoagulant usage

Of 139 patients who received appropriate methods of VTE prophylaxis, 100% of patients received 40 mg of enoxaparin once daily, which was considered appropriate according to the standard recommendations and the patients' condition. However, the first dose was given more than 12 hours after the surgery, which was later than the recommendations. The rate of patients had a shorter duration of prophylaxis than recommendation was 96.4%. Of those, 129 (92.8%) patients in the high-risk group with major surgery used less than 25 days, and 5 (3.6%) patients in the moderate-risk group used less than 7 days (Table 2).

***Table 2**: The appropriateness of pharmacologic thromboprophylaxis (N=139)*

Variables		**n (%)**
Method	Pharmacologic	139 (100%)
Dose	Appropriate	139 (100%)
	Inappropriate	0
Initial time	Appropriate	0
	Inappropriate (late)	139 (100%)
Duration	Appropriate	5 (3.6%)
	Shorter than recommended	131 (96.4%)
	Less than 7 days at moderate risk	5 (3.6%)
	Less than 25 days at high-risk	129 (92.8%)
	Longer than recommended	0

DISCUSSIONS

This was the first study in Vietnam that evaluated thromboprophylaxis after surgery in colorectal cancer patients. The appropriateness of the prophylaxis, including the method of prophylaxis, drug selection, dosage, and prophylactic duration, was determined following the current practical guidelines.

The proportion of patients receiving appropriate prophylaxis in our study was 83.7%. This is relatively higher than the thromboprophylaxis rate in Amin's study in the US in 2010 and Hoang Bui Hai's study in 2014 (58.3% and 22.8%, respectively) [1,7]. Postoperative colorectal cancer patients are often categorized as being at higher risk of VTE. Therefore, the thromboprophylaxis rate could be higher among them.

All patients with appropriate prophylaxis in the current study were prescribed 40 mg of enoxaparin once daily, with the first dose given more than 12 hours postoperatively. Enoxaparin is the first-recommended LMWH for VTE prophylaxis after cancer surgery because it has sufficient evidence for safety, efficacy, and convenience [5,6,8,10,12,14]. However, the guidelines are not completely unified on the time to initiate the drug; most treatment guidelines recommend anticoagulation before surgery, and the VNHA guidelines recommend between 6 and 12 hours after surgery. Therefore, we considered the time of drug initiation more than 12 hours after the surgery inapproriate as it is later than the recommended time by all current guidelines.

In our study, extended-duration VTE prophylaxis was not used in the majority of surgeries. Among surgeries following by an appropriate postoperative anticoagulant, 94.6% had a shorter prophylactic duration than recommendations. Unchanged prescribing habits of surgeons or their unawareness of importance of extended-duration thromboprophylaxis for colorectal cancer patients may be main factors contributing to the high rate. According to the ENOXACAN II clinical trial, for high-risk major abdominal and pelvic surgery, prophylaxis with enoxaparin of 40 mg (equivalent to 4000 UI) for 6-10 days without prolongation duration of up to 4 weeks increased the risk of VTE more than 2-fold (12.0% and 4.8% during the dosing period; 13.8% and 5.5% within 3 months) [2]. Thus, prolonged prophylaxis is recommended to significantly reduce the risk of VTE for the patient without increasing the bleeding risk. The lack of prolonged VTE prophylaxis in high-risk pelvic surgery patients was a gap in clinical practice not only in Vietnam but also in other countries around the world. In the US, the rate of prolonged prevention in colorectal cancer surgery patients in 2017-2018 was 16.8%. Extended-duration thromboprophylaxis for patients concentrated mainly in large hospitals and tended to increase gradually over time, but adherence remains low [13].

Studies on VTE prevention after surgery in Vietnam and around the world have shown that the proportion of patients with appropriate methods of thromboprophylaxis, drug indication, dosage, and duration is relatively low, especially in those undergoing non-orthopedic surgery. This rate in Amin's study in the US in 2010 was 7.5%, while the lowest rate of less than 1% was seen in the ENDORSE study in 2008 in many different countries [1,3]. In the study of Hoang Bui Hai in a hospital in Vietnam in 2014, the rate was 0% (5 patients with appropriate prophylaxis were in the orthopedic surgery group) [8]. Our study, with a focus on post-operative colotectal cancer patients, who are a special group in non-orthopedic surgery, demonstrated the significant gap between evidence-based thromboprophylaxis recommendations and clinical practice in reality.

The main limitation of our study was the retrospective method of data collection using information from medical records to assess the risk status and appropriateness of

thromboprophylaxis. While it could be an efficient method during the complicated COVID-19 epidemic, certain risk factors cannot be fully assessed based on medical records. This may have led to inaccurate evaluations about a patient's risk status or the appropriateness of thromboprophylaxis regimens. Further prospective study should be done to address this issue and to better assess the thromboprophylaxis in cancer patients after surgery.

CONCLUSIONS

Postoperative prophylaxis of VTE among colorectal cancer patients has been widely applied in clinical practice. However, inappropriate prophylaxis, such as lack of thromboprophylaxis, late initiation of anticoagulants, and lack of prolonged prophylaxis in high-risk patients, was still a major gap that limited the effectiveness of thromboprophylaxis. Further studies on the views of clinical practitioners should be done to bring more insight to the practice of VTE prophylaxis so that suitable measures can be proposed to improve prophylaxis practice and patient outcomes.

CONFLICTS OF INTEREST

It is confirmed that there will be no conflict of interest to arise.

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