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Practice patterns of VTE chemoprophylaxis after discharge following hepatic and pancreatic resections for cancer: A survey of hepatopancreatobiliary surgeons

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Abstract

Patients with hepatopancreatobiliary (HPB) malignancies undergoing resection are prone to venous thromboembolism (VTE), and current guidelines recommend up to 28 days of chemoprophylaxis after major surgery. We sought to determine the practice patterns among HPB surgeons for use of chemoprophylaxis after discharge. A survey on VTE chemoprophylaxis after oncologic HPB operations was distributed to attending surgeons at the 18 HPB fellowship training programs in the United States and Canada. Of the HPB surgeons surveyed, 44 (44%) responded. VTE prophylaxis is used by 93% of respondents in the inpatient postoperative setting. Chemoprophylaxis after discharge for pancreaticoduodenectomy and distal pancreatectomy is utilized by 45% and 39% of respondents, respectively. Of those who prescribe chemoprophylaxis after discharge, 79% and 88% prescribe it for the recommended 28 days after pancreaticoduodenectomy and distal pancreatectomy, respectively. Chemoprophylaxis after discharge for major and minor hepatectomy is utilized by 39% and 26% of respondents, respectively. Of those who prescribe chemoprophylaxis after discharge, 67% and 55% provide it for the recommended 28 days after major and minor hepatectomy, respectively. Despite documented prolonged postoperative thrombotic risk, the use of chemoprophylaxis following discharge after pancreatic and liver resections for cancer was moderate among surveyed HPB surgeons.

Keywords

Venous thromboembolism; Surgery; Survey; Chemoprophylaxis; Cancer

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Conflict of interest All authors declare that they have no conflicts of interest.

Ethical approval There were no animals used in this study. Survey results were collected from human (respondents) anonymously. This survey was approved by the Office of Human Subjects Research Protections and was determined not to need an IRB. A consent statement was included in the email that went to every respondent stating that by participating in the survey they consented to have their results included in this study.

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Introduction

Venous thromboembolism (VTE), including both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major source of morbidity and mortality for patients suffering from cancer [1–4]. There are several well-established risk factors for VTE which include a diagnosis of cancer, involvement in trauma, fracture of pelvis, hip or long bones, pregnancy, immobility, and abdominal or pelvic surgery [3–7]. Interestingly, a large proportion of VTE events in patients with cancer are diagnosed in the outpatient setting [7, 8]. In a study of post-operative patients with cancer, 40% of VTE events occurred more than 21 days after the operation, while the mean length of stay for the study population was 6–12 days [7]. As such, the use of extended pharmacologic VTE prophylaxis for 28 days following surgery has been carefully examined. In a randomized study of cancer patients having undergone abdominal or pelvic surgery, the use of prolonged chemoprophylaxis was associated with a 4.8% risk of VTE compared to 12% in those who received prophylaxis only during the inpatient period [9]. Another clinical trial revealed that extended chemoprophylaxis after surgery was associated with a greater than 50% reduction in venographic VTE in patients undergoing any major abdominal surgery [10].

The current National Comprehensive Cancer Network (NCCN) guidelines for cancer-associated VTE support the administration of chemoprophylaxis for up to 28 days post-operatively in patients undergoing major abdominal or pelvic surgery for gastrointestinal malignancies [11]. A review of almost 6600 patients who underwent an operation related to their hepatopancreatobiliary (HPB) malignancy in the NSQIP database noted a VTE rate of 3.6% after surgery, of which 32.5% occurred after discharge. This was the second highest rate among solid tumor histologies [12]. Despite these evidence-based recommendations, extended 28-day VTE prophylaxis likely remains underused. While a large proportion of HPB surgeons use inpatient VTE prophylaxis, only 14% of surgeons routinely discharged patients home on pharmacological prophylaxis after hepatic resection, irrespective of a diagnosis of cancer [13]. Currently, there is little data accurately describing the use of VTE prophylaxis after discharge for patients undergoing an HPB resection for cancer. We designed and distributed a survey to the attending faculty at each of the 18 HPB fellowship training programs in the United States and Canada. We sought to determine the practice patterns relating to inpatient and post-discharge VTE prophylaxis following oncologic HPB operations.

Methods

The survey consisted of 14 multiple choice questions and was created using the platform [surveyplanet.com](https://www.surveymonkey.com). It was designed to be completed in under 3 min. It aimed to delineate the pattern of prescribing VTE chemoprophylaxis upon discharge from oncologic HPB surgery. The survey can be found in the supplemental materials as Fig. 1. This study was approved by the National Institutes of Health.

We opted to distribute the survey to the attending surgeon staff at the HPB fellowship training programs. We chose to survey this group of surgeons given that they generally practice at high volume centers and because their practice patterns likely influence the next

generations of HPB surgeons. Given this decision, we requested approval from the Americas Hepatopancreatobiliary Association (AHPBA) research committee, which was granted without further provision. Invitations to take the survey were sent by email, with a reminder sent out 2 and 3 weeks following the initial message. The email described the project and provided a link to the survey. Participation in this survey was voluntary and anonymous. No financial incentive was offered.

All comparisons of categorical variables were completed with a chi square analysis. Statistical significance was accepted with 95% confidence. All analyses were performed using SPSS version 25.

Results

The questionnaire was completed by 44 of the 100 HPB faculty surgeons surveyed between March and April 2018, representing a 44% response rate. Respondents were from all regions of the United States and Canada, with the highest percentage coming from the Midwest (n= 14, 32%). The region in which respondents practice did not show a significant association with the use of chemoprophylaxis. In the inpatient setting, 93% (n = 41) of respondents use both mechanical and chemical prophylaxis for patients undergoing hepatic and pancreatic resections for cancer. In addition, 68% (n = 30) of the respondents ensure that the first dose of chemoprophylaxis is administered within two hours of anesthesia induction. For chemoprophylaxis, enoxaparin is the agent of choice during the inpatient setting 57% (n = 25) of the time. Of the 20 surgeons who send their patients home with chemoprophylaxis, 65% (n= 13) consistently discharge patients on chemoprophylaxis for all operations that they perform. The agent utilized in the outpatient setting was enoxaparin 64% (n = 28) of the time, rivaroxaban 5% (n = 2) of the time, subcutaneous heparin 2% (n= 1) of the time, and no chemoprophylaxis at discharge 30% (n= 13) of the time (Table 1).

Pancreatic operations

The majority of respondents (56%, n = 24/43) do not routinely discharge patients on VTE chemoprophylaxis following a Whipple operation, while 61% (n = 25/41) do not after a distal pancreatectomy (Fig. 1). Of the respondents that prescribe chemoprophylaxis after discharge, 79% (n= 15/19) and 88% (n = 14/16) do so for the recommended 28 days after Whipple and distal pancreatectomy, respectively (Table 2). There was no significant difference between rates of chemoprophylaxis after Whipple vs distal pancreatectomy.

Liver operations

The majority of respondents (64%, n = 27/42) do not routinely discharge patients on VTE chemoprophylaxis following a major hepatectomy, while 74% (n = 31/42) do not after a minor hepatectomy (Fig. 1). Of the respondents that prescribe chemoprophylaxis after discharge, 67% (n= 10/15) and 55% (n = 6/11) do so for the recommended 28 days after major and minor hepatectomy, respectively (Table 3). There was no significant difference between rates of chemoprophylaxis after major vs minor hepatectomy.

Insurance coverage as a potential barrier

Half of respondents (50%, n = 22/44) felt that medication coverage was a barrier to outpatient VTE chemoprophylaxis, while 30% of respondents (n= 13/44) did not feel that insurance issues posed any barrier, and 18% (n = 8/44) of respondents were “not sure.” One respondent left this question blank. Of the respondents that indicated insurance as a barrier to VTE prophylaxis after discharge, 50% (n = 11/22) did not prescribe chemoprophylaxis upon discharge after any of the HPB operations queried in this study. Of the respondents that indicated insurance was not a barrier to VTE prophylaxis after discharge, 69% (n = 9/13) prescribed chemoprophylaxis upon discharge after HPB operations queried in this study.

Discussion

Abdominal surgery and cancer represent independent and well-established risk factors for VTEs [3–7]. Given the morbidity and mortality associated with VTE events, the current NCCN guidelines recommend up to 28 days of VTE chemoprophylaxis for patients with gastrointestinal malignancies undergoing major abdominal or pelvic surgery [11]. Despite this recommendation, little data exists regarding adherence to these guidelines. In fact, a single prior study assessed the practice patterns for VTE chemoprophylaxis after discharge following liver resection for any indication, and reported 14% compliance among respondents [13]. Given the especially high rate of VTE events reported in patients undergoing pancreatic and hepatic oncologic resections, insight into current practices relating to post discharge VTE chemoprophylaxis are of particular interest. We therefore designed and distributed a VTE chemoprophylaxis survey to faculty at the HPB fellowship training programs. In doing so, we have identified that, though the vast majority of HPB surgeons ensure that patients are placed on VTE chemoprophylaxis post-operatively, fewer than half continue VTE prophylaxis after discharge.

Abdominal surgery is an independent risk factor for VTE, and is thought to induce a hypercoagulable state that can last for at least 14 days [14]. Measured fibrin monomers and fibrin-D-dimers in the plasma of patients in the pre, peri, and postsurgical periods demonstrated that all patients had elevated levels for 14 days after the operation [15–17]. Additionally, malignant cells release procoagulants (e.g. tissue factor), generate a proinflammatory state, disrupt naturally occurring inhibitors like protein C or S, and can directly invade and compress vessels [18]. A VTE event is known to delay treatment, increase the risk of recurrent thromboembolic events, result in bleeding complications from anticoagulation therapy, increase mortality, increase healthcare costs, and decrease quality of life [19–21]. Clearly, VTE events should be avoided or prevented, if feasible, in the interest of achieving optimal outcomes for patients.

More than half of the respondents in this study do not send patients home on VTE chemoprophylaxis at the time of discharge. We considered several factors that could contribute to these findings. First, the NCCN guideline language is somewhat vague in stating chemoprophylaxis should be given for “up to 28 days” after surgery, leaving room for interpretation. The most convincing data cited in support of the guideline are two randomized clinical trials that were mentioned earlier in this paper [9, 10]. While each of

these trials demonstrated a decreased rate of VTEs with extended chemoprophylaxis after surgery, neither focused specifically on HPB operations. A wide range of operations were included in both trials, including colorectal, gastric, biliary, pancreatic, genitourinary tract, and gynecologic. Second, there is often a delay or gap between guideline updates and changes in medical practice. The NCCN guidelines included these recommendations about extended VTE chemoprophylaxis in 2007 [22, 23]. A review of 500 hospital patients in 2015, both surgical and medical, found that only 45% had received thromboprophylaxis in compliance with inpatient guidelines [24]. A single institution study in 2014 (7 years after the guidelines were changed) noted that 79% of the colorectal surgery units and 48% of HPB surgery units were compliant with prescribing VTE chemoprophylaxis upon discharge. After these baseline statistics were collected, the hospital educated the physicians on updated guidelines and placed visual cues on each unit. Subsequently, an improved compliance rate of 93% for colorectal units and 72% for HPB units was noted [25]. Finally, perceived barriers to prescribing chemoprophylaxis upon discharge could be contributing to low adherence. One barrier that is commonly cited is insurance status and consternation over medication coverage. A study at MD Anderson looked at the cost of prophylactic enoxaparin prescription after discharge from major abdominal/pelvic surgery for gynecologic malignancies. The mean out of pocket cost for patients with private insurance was \$62 USD, \$102 USD with medicare, and \$970 USD without insurance. In addition, 10% of patients needed prior insurance authorization (which can take a couple days) before getting assistance paying for the prescription [21]. We found that half the respondents felt insurance was a barrier to discharging patients on chemoprophylaxis.

Pancreatic cancer is associated with one of the highest rates of VTE events when compared to other solid tumors. A retrospective review of over one million patients with cancer demonstrated a VTE rate of 8.1% for hospitalized patients suffering from pancreas cancer [4]. Following a pancreatic resection, complications such as hemorrhage or pancreatic leak can be devastating. Several studies have established that a pancreatic leak or fistula postoperatively constitutes a risk factor for a delayed hemorrhage, presumably because the leak can lead to abscess formation and weaken the surrounding tissue and blood vessels, thereby increasing the potential for hemorrhage [26–28]. The rate of pancreatic fistula after pancreaticoduodenectomy and distal pancreatectomy has been reported to be as high as 28% [29, 30]. As such, if a patient were to develop a VTE and need to be placed on therapeutic anticoagulation, they may be at increased risk for bleeding in the setting of a leak [31]. Therefore, the potential for complications of a VTE and the treatment it entails in patients undergoing pancreas resections may be particularly severe, which may be reflected in our study with more respondents opting for post-discharge chemoprophylaxis after a pancreatectomy than a liver resection.

In the early postoperative period after liver resections, routine bloodwork commonly reveals an increase in prothrombin time (PT) and international normalized ratio (INR), and a fall in platelet count, suggesting a transient hypocoagulable state. However, recent evidence suggests an increase in the risk of VTE events after a major hepatic resection despite these biochemical and hematologic abnormalities [32]. A NSQIP review of 5500 patients found an overall incidence of VTE of 2.9% after hepatic resection, with a higher rate following right hepatectomy (4.2%), and extended resection (5.8%). This same study demonstrated that the

risk of VTE outweighed the risk of postoperative bleeding in the first 30 days after surgery [33]. In a separate review, pharmacologic thromboprophylaxis was associated with a lower rate of symptomatic VTEs and post operative red blood cell transfusion for patients undergoing major hepatectomy, highlighting the safety of chemoprophylaxis in post operative patients after hepatic resection. Interestingly, no difference was detected in VTE rates for malignant and benign conditions after a hepatic resection, suggesting the risk is likely related to the resection itself [34]. The bleeding risk after a liver resection is highest in the immediate perioperative period. Since this risk drops over time, the concern for bleeding after an operation should not be a deterrent to sending patients home on VTE chemoprophylaxis, barring any extenuating circumstances in patients who have bleeding disorders.

Our study carries some of the inherent limitations of a survey study. First, it only captured part of the population of HPB surgeons. We specifically targeted faculty surgeons at HPB fellowship programs so that we would be surveying those who perform these operations often and at high volume centers. However, this excludes many HPB surgeons across the country. Secondly, we have a response rate of 44%. Surgeons who tend to prescribe VTE prophylaxis may have been more motivated to respond to our survey, thereby creating a selection bias. Finally, there is no way to correlate the survey results with actual medical practice.

Our study demonstrates that despite the guideline recommendations, the majority of responding HPB surgeons do not prescribe chemoprophylaxis to patients upon discharge after pancreatic and liver resections for cancer. Although multicenter randomized clinical trials specifically targeting the patient population are lacking, the available data suggests chemoprophylaxis is safe and that VTE events are a source of major morbidity. There are certainly more unanswered questions pertaining to VTE and prevention than answerable, but we hope this data will provide a relevant framework for future studies addressing this important topic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Current guidelines recommend up to 28 days of chemoprophylaxis after major surgery for cancer.
- Survey study of practice patterns of surgeons at HPB training programs.
- Chemoprophylaxis after discharge for pancreaticoduodenectomy and distal pancreatectomy is utilized by 45% and 39% of respondents, respectively.
- Chemoprophylaxis after discharge for major and minor hepatectomy is utilized by 39% and 26% of respondents, respectively.
- Despite documented prolonged postoperative thrombogenic risk, the use of chemoprophylaxis following discharge after pancreatic and liver resections for cancer was moderate among surveyed HPB surgeons.

Fig. 1.

Percent of hepato-pancreato-biliary surgeons from fellowship training programs who prescribe VTE chemoprophylaxis after discharge

Table 1

Characteristics and overall practices of respondents

Characteristic	Number n = 44 (%) ^b
Region of country	
West	9 (20)
Midwest	14 (32)
South	9 (20)
Northeast	5 (11)
Canada	7 (16)
Type of prophylaxis used	
Mechanical only	1 (2)
Chemical only	2 (5)
Both mechanical and chemical	41 (93)
Type of chemoprophylaxis used in hospital	
None	1 (2)
Enoxaparin	25 (57)
Subcutaneous heparin	18 (41)
Timing of first dose of chemoprophylaxis	
None	1 (2)
At home preoperatively	1 (2)
Within 2 h of anesthesia induction	30 (68)
6 h postoperatively	5 (11)
24 h postoperatively	7 (16)
Type of chemoprophylaxis used after discharge	
None	13 (30)
Enoxaparin	28 (64)
Subcutaneous heparin	1 (2)
Rivaroxaban	2 (5)
Prescribe chemoprophylaxis after discharge following all HPB operations in question ^a	13 (30)
Insurance coverage is a barrier to chemoprophylaxis after discharge	
Yes	22 (50)
No	13 (30)
Not sure	8 (18)
Unanswered	1 (2)

^a operations include Whipple, distal pancreatectomy, major hepatectomy, and minor hepatectomy^b Rounded to nearest percentage

Table 2

Use of VTE chemoprophylaxis after discharge following pancreatic resection

Operation ^a	Discharge with chemoprophylaxis N (%) ^c	Duration of chemoprophylaxis N(%) ^{b,c}	
Whipple (n = 43)	19 (44)	< 28 days	4 (21)
		28 days	15 (79)
		> 28 days	0
Distal pancreatectomy (n = 41)	16 (39)	< 28 days	2 (13)
		28 days	14 (88)
		> 28 days	0

^a Respondents who selected “I do not perform this operation” were excluded from the above analysis^b Percentage of respondents who discharge patients with chemoprophylaxis^c Rounded to nearest percentage

Table 3

Use of VTE chemoprophylaxis after discharge following liver resection

Operation ^a	Discharge with chemoprophylaxis N (%) ^c	Duration of chemoprophylaxis N(% ^b) ^c	
Major hepatectomy (n = 42)	15 (36)	< 28 days	4 (27)
		28 days	10 (67)
		> 28 days	1 (7)
Minor hepatectomy (n = 42)	11 (26)	< 28 days	4 (36)
		28 days	6 (55)
		> 28 days	0

^a Respondents who selected “I do not perform this operation” were excluded from the above analysis^b Percentage of respondents who discharge patients with chemoprophylaxis^c Rounded to nearest percentage