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The incidence of clinically significant venous thromboembolism in an Asian population after major hepatobiliary and pancreatic surgery

B.C. Toh, T.C.Y. Pang, W.W.L. Woon, D.X.W. Yeo, Y.Z. Lee, S.P. Junnarkar, J. K. Low

ABSTRACT

Introduction: The incidence of venous thromboembolism (VTE) is not well defined in Asian population after major hepatobiliary and pancreatic (HPB) surgery. The use of pharmacological prophylaxis is debatable due to postoperative coagulopathy. Aim: To determine the incidence of clinically significant VTE events in Asian undergoing major HPB surgery. Methods: A retrospective review of patients undergoing major HPB surgery between January 2010 to August 2013 at Tan Tock Seng Hospital, Singapore was conducted. Clinical notes and radiology reports were reviewed to screen for patients who developed VTE. A secondary end-point was 30-day and 90-day mortality. Results: 224 patients had major HPB surgery with median age of 61 years and BMI of 22.3. 143 patients were male. Majority of the patients were Chinese and most underwent open hepatic surgery for malignancy. A few had a past history of VTE. No patient developed DVT, whilst a single patient was diagnosed with pulmonary embolus. There were two unexpected deaths within 90 days of surgery and neither appeared to be VTE-related. Statistical tests comparing our results with reported baseline VTE risk in literature and risk with chemoprophylaxis would suggest the low incidence found in this study was comparable to Western patients given chemoprophylaxis. Conclusion: The risk of VTE appears low in Asian patients undergoing major HPB surgery. Hence, one must consider if the benefits of low molecular weight heparin does indeed outweigh the risks.

Keywords: Asian, Venous thromboembolism, Major hepatobiliary surgery, Incidence

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INTRODUCTION

The incidence of venous thromboembolism (VTE) is not well defined in the Asian population. Epidemiological

studies have suggested that the VTE incidence in the Asian population is less than that of the Caucasian population, but not quite as low as previously thought [1]. The use of pharmacological prophylaxis after hepatic surgery is also debatable, with many surgeons taking a very cautious take on its use due to the possibility of postoperative coagulopathy [2]. On the other hand, a study looking at comparative rates of VTE incidence with different types of surgeries has suggested that HPB surgery is in fact associated with one of the highest rates of VTE [3]. Physiologically, this is unsurprising given the presence of malignancy, the relatively long duration of surgery and length of stay as well as the severity of the physiological insult.

Unfortunately, the incidence of VTE in this subgroup of patients has been poorly studied, with the majority of VTE studies in abdominal surgery focusing on pelvic, colorectal and upper gastrointestinal surgery. Recent systematic review suggest that the risk of VTE in Asian general surgery patients is low, even in the context of risk factors typically regarded as high risk [4]. The aim of this study was therefore to determine the incidence of clinically significant VTE events in patients undergoing major hepatobiliary and pancreatic (HPB) surgery in a tertiary institution.

MATERIALS AND METHODS

A retrospective review of consecutive patients undergoing major HPB surgery at Tan Tock Seng Hospital, a tertiary institution in Singapore, was conducted. The study period was from 1st January 2010 to 31st August 2013. Patients were identified by searching through the unit's operative database. Inclusion criteria included all patients who underwent (a) any form of liver resection; (b) any form of pancreatic resection; (c) any form of resection involving the common bile duct/ hepatic duct; (d) any form of biliary bypass; (e) any form of surgery for hepatic cysts or hydatid disease. Excluded were patients who underwent cholecystectomy, including bile duct exploration; liver biopsy; staging laparoscopy and patient who had their procedure abandoned due to locally advanced or metastatic disease. All patients had mechanical VTE prophylaxis with external pneumatic calf compression perioperatively for 24 to 48 hours followed by TED (thromboembolic deterrent) stockings for the duration of hospital stay. All patients underwent postoperative ambulating protocol - Sit out of bed at postoperative day 1 and ambulation with assistant at postoperative day 2. Only patients with a past medical history or a strong family history of VTE were given pharmacologic VTE prophylaxis.

Clinical notes and all radiology reports of these patients were reviewed to screen for patients who developed VTE during and after their admission. Relevant VTE were defined as symptomatic upper or lower limb deep vein thrombosis (DVT) and pulmonary embolism (PE). A secondary end-point was 90-day mortality, with particular emphasis on patients who died unexpectedly. This is important because in a clinical environment where VTE is perceived as uncommon, there is a higher likelihood of missing VTE as a complication. Therefore, unexpected postoperative deaths may represent a missed clinically significant VTE incident.

Other clinical characteristics collected included demographic characteristics (age, gender, race), VTE risk factors (such as body mass index (BMI), past history of VTE, malignancy status), length of ICU and hospital stay as well as operative details (such as nature of operation, operative duration, open or laparoscopic status, perioperative mechanical or pharmacological VTE prophylaxis). Patients with 30-day and 90-day mortality after major hepatobiliary surgery were identified and their case notes were reviewed to assess possible VTE as the cause of death. The VTE risks of these patients were assessed retrospectively by calculating the Caprini Risk Score according to the information available in the case notes. The Caprini Risk Score is a scoring system which predicts a patient's VTE risk according to the presence of risk factors.

All statistical analyses were performed using Stata SE version 11.2 for Windows (TX, USA). Descriptive statistics were presented as n(%) or median values (IQR interquartile range) unless otherwise stated. To compare our VTE risks with that found in literature, one sampled tests of proportions were used.

RESULTS

Between January 2010 and August 2013, 1199 HPB operations were performed. Of these, 224 fulfilled the criteria of major HPB surgery and these patients formed the cohort analyzed in this study. The median age was 61 years and 143 patients were male. Table 1 summarizes the characteristics of the study cohort. In brief, the majority of patients were Chinese and most underwent open hepatic surgery for malignant pathology. The patients were relatively lean, with the median BMI being 22.3. Few had a past history of VTE and the median length of stay was relatively long at 9 days, although ICU stay was uncommon.

Of the 224 patients in this study, no patient developed symptomatic DVT, whilst a single patient was diagnosed with pulmonary embolism without evidence of DVT. The characteristics of these patients with VTE are summarized in Table 1 and Table 2. Whilst not specifically determined as an outcome endpoint, two patients were found to have inferior vena cava thrombosis. Case note review showed that one of the two patients had extensive inferior vena cava (IVC) thrombosis after spleen preserving distal pancreatectomy for a neuroendocrine tumor. This might have been related to an IVC filter inserted prior to surgery for treatment of his preoperative common femoral DVT. The other patient developed IVC thrombosis after a right hepatectomy for colorectal liver metastases.

Table 1: Summary of characteristics of patients who underwent major HPB operations

	Median (IQR Q1-Q3) or n(%)	
	All patients (*n*=224)	**Patients with actual or suspected VTE (*n*=5)**
Basic characteristics		
Age (years)	61 (IQR 54–69)	63 (IQR 59–66)
Male sex	143 (64)	3 (60)
Race		
Chinese	188 (84)	4 (80)
Malay	14 (6)	1 (20)
Indian	6 (3)	0 (0)
Others	16 (7)	0 (0)
Operative characteristics		
Type of Surgery		
Hepatic	126 (56)	3 (60)
Pancreatic	79 (35)	2 (40)
Biliary	19 (9)	0 (0)
Operation time (hours)		
Overall	5.3 (IQR 4.5–8.3)	5.8 (IQR4.3-7.0)
Hepatic	5.3 (IQR 3.9–7.3)	7.0 (IQR4.7-9.8.0)
Pancreatic	7.9 (IQR 6–9.4)	5.0 (IQR4.7-5.4)
Biliary	6.1 (IQR 4.2–7.6)	-
Surgical approach		
Laparoscopic	38 (17)	0 (0)
Open	172 (77)	5 (100)
Conversion	14 (6)	0 (0)
VTE risk factors		
Malignant disease	162 (73)	5 (100)
BMI (kg/m2)	22.3 (IQR 19.7–25.4)	24.7 (IQR 23.6–25.5)
VTE prophylaxis		
Pharmacological	7 (3)	1 (20)
Mechanical	224 (100)	5 (100)
Past history or Family History of VTE		
DVT	6 (2.7)	0 (0)
PE	1 (0.5)	1 (20)
Length of stay (days)		
Overall	9 (IQR 6–14.25)	13 (IQR 10–26.5)
ICU	0 (IQR 0–0)	0 (IQR 0–0)
Total Caprini Risk Score		
Very Low (0)	0 (0)	0 (0)
Low (1–2)	2 (1)	0 (0)
Moderate (3–4)	38 (17)	0 (0)
High (> 5)	184 (82)	5 (100)

Abbreviations: IQR, Inter Quartile Range; Q1, 1st Quartile; Q3, 3rd Quartile; BMI, Body Mass Index; DVT, Deep Vein Thrombosis; HPB, Hepatobiliary and Pancreatic Surgery; ICU, Intensive Care Unit; PE, Pulmonary embolism; VTE, Venous Thromboembolism.

Table 2: VTE cases, actual or suspected, diagnosed during study period (*n*=5)

Deep Vein Thrombosis	0 (0%)
Pulmonary Embolism	1 (0.4%)
Inferior Vena Cava Thrombosis	2 (0.9%)
Unexpected Death	2 (0.9%)

Abbreviations: VTE, Venous Thromboembolism Values

VTE risk factor assessment based on Caprini Risk Score was calculated for all patients in the cohort study [4]. The majority of patients (82%) were classified as high risk (total Caprini Risk Score >5). The 5 patients who developed VTE or sudden death were all classified as high risk. This is also summarized in Table 1. A total of 8 patients with past medical history or strong family history of VTE were given pharmacologic VTE prophylaxis. There were no postoperative hemorrhage complications noted.

To ensure potential PE cases were not missed, 30-day and 90-day mortality were examined. The total number of 30-day mortality was 3 (1.35%) and 90-day mortality was 9 patients (4.03%). 7 out of the 9 patients had cause of death identified as summarized in Table 3. The two unexpected deaths with unknown cause of death were sent for coroner's case. A brief summary of each of these deaths was described in Table 4. It would seem unlikely that these patients died from a VTE related cause based on clinical information available on case-notes. However, no postmortem autopsy was performed to definitively exclude this.

According to Bahl et al., the incidence of VTE of 8216 patients from NSQIP data in high risk patients (Caprini score ≥5) was 1.94% and the estimated baseline risk without chemoprophylaxis was 6%. This can be compared to the results of our current study. We found 1 case of pulmonary embolism and 2 cases of inferior vena cava (IVC) thrombosis of which one was from pre-existing VTE and 2 cases of unexpected death. This gives an actual rate of VTE of 2 cases (0.89%) (one IVC thrombosis should be excluded as it was from pre-existing VTE) and at worst case scenario up to 5 cases (2.2%). Using a one sample test of proportions (two-sided test), even assuming the worst case scenario of 2.2% incidence, the VTE risk found in this study was still significantly less than the 6% baseline risk reported by Bahl (p = 0.0166). Furthermore, one can also set up a non-inferiority test. If we take the NSQIP data of 1.94% and used a margin of 1%, a one-sided test of proportions using actual VTE incidence in this study would yield a p-value of 0.0349. Taken together, these tests would suggest that the observed VTE rates without routine chemoprophylaxis in this study is better than VTE risks observed in the West without chemoprophylaxis and possibly equivalent to the risk with chemoprophylaxis [5, 6].

Table 3: 30-day mortality and 90-day mortality of patients who underwent major HPB operations (n = 9)

Mortality	Cause of Death n (%)				Total
	Unexpected Death	Ischemic Bowel	Pneumonia	Liver Failure	
30-day Mortality	2 (0.90%)	1 (0.45%)	-	-	3 (1.35%)
90-day Mortality	2 (0.90%)	1 (0.45%)	5 (2.23%)	1 (0.45%)	9 (4.03%)

Abbreviations: HPB Hepatobiliary and Pancreatic Surgery

Table 4: Brief summary of unexpected death patients. (n=2)

	Age/Race/ Sex	Comorbidities	BMI	Final Histopathology	Operation	Clinical Course
Sudden Death 1	43/Chinese/ Male	Hepatitis B Child A Liver Cirrhosis	23.6	Rectal Mucinous Adenocarcinoma with Hepatocellular carcinoma.	Abdominal-Perineal Resection, synchronous multiple wedge resections of segment 4a, 7 and 8 for suspected liver metastases and vertical rectus abdominis myocutaneous flap for perineal cover.	Complicated by postoperative intraabdominal haemorrhage from Abdominal-Perineal and Liver resections site, bowel ischaemia and acute liver decompensation. CT-pulmonary angiogram done POD 4 did not show any evidence of pulmonary embolism. Died POD 10.
Sudden Death 2	59/Malay/ Female	Obesity Hypertension Hyperlipidaemia	35	Gallbladder carcinoma.	Right Hepatectomy, cholecystectomy and hepatojejunostomy.	Complicated by postoperative hypotension likely from stress induced myocardial infarction. Liver decompensation ensued. Died POD day 3.

Abbreviations: BMI Body Mass Index, POD Postoperative Day

DISCUSSION

The incidence of venous thromboembolism (VTE) has long been thought to be rare in Asian patients after major operations. However, there are evidences to suggest that it does occur as previously reported by Chew et al. and Satoh et al. mainly focused on cancer-related VTE among Taiwanese and Japanese, although at a lower rate than in the Caucasian population [7–9]. This is consistent with literature that common genetic polymorphisms, such as Factor V Leiden and prothrombin G20210A, and environmental risk factors, such as obesity, may account for increased risk in European population [10].

Our current study has found only one case of confirmed PE (0.4%), as well as two cases of IVC thrombosis (0.9%), in 224 patients undergoing major HPB surgery regardless of benign or malignant disease. Two (0.9%) cases of unexpected postoperative mortality were noted also although it would seem unlikely that either of these would have been caused by a massive pulmonary embolism. Such low rates were found despite the fact that vast majority (82%) of patients were classified as high risk (based on Caprini Risk Score) and the majority did not receive VTE pharmacoprophylaxis (Table The majority of VTE occurred in patients who had undergone surgery for malignancy (83% versus 17% for benign disease). This is consistent with literature, where both the presence of a malignancy (especially in advanced stage) was associated with the development of postoperative VTE [11].

One of the limitations of our study is that it is a retrospective study, thus it is based on patient's symptoms of DVT and PE. The incidence of VTE may therefore be lower than if screening of all patients for VTE was performed. However, the significance of asymptomatic VTE detected on screening is controversial. In addition, HPB surgery is a heterogeneous entity with certain operations likely carrying a higher risk of VTE due to their differing operative times, postoperative course as well as the incidence of underlying malignancy. We have attempted to homogenize this study population by using a clearly defined inclusion criteria to select only patients who have undergone major HPB surgery.

While the 9th edition of ACCP (American College of Chest Physicians) guidelines consider malignancy as a risk factor regardless of primary location, postoperative VTE rates may in fact vary depending on the type of major operation performed [12]. Mukherjee et al. found that the incidence of VTE was 1.76% in patients undergoing hepatectomy and 2.91% in patients undergoing pancreatectomy respectively. Furthermore, the odds of developing VTE for these operations were found to be more than twice (OR 2.55 and 2.07 respectively) that of bariatric surgery patients [3]. Unfortunately, no data exists in literature on the incidence of VTE in HPB surgery patients in Asian patients. The majority of Asian VTE general surgery studies were on either colorectal or gastric cancer surgery patients, with no study examining VTE risk in HPB patients exclusively [13].

In contrast, a recent study on a Caucasian population found the incidence of DVT and PE in HPB patients to be 0.97–3.3%, and 1.7–1.8% respectively. This is despite the majority of them receiving chemoprophylaxis [14, 15]. This risk level, and also the risk reported by Mukherjee et al. [3] would justify our use of 2% with a 1% margin as a basis or our non-inferiority test. We have found in this test that our reported rates without chemoprophylaxis is not worse than that reported in the West in patients receiving chemoprophylaxis.

Finally, while low molecular weight heparin (LMWH) prophylaxis has been shown to be safe and effective in the Western population [16], it is not entirely without risk. Studies on Asian patients have shown increased rates of complications in the LMWH group compared to non LMWH group. These ranged from small hematomas and minor ooze to major intra-abdominal and intraluminal bleeding [17, 18]. Interestingly though, studies which used LMWH in Asian patients invariably demonstrated a zero rate of symptomatic VTE [13]. However, it is estimated that the number needed to treat to prevent one symptomatic VTE and PE to be 70 and 140 respectively [13].

CONCLUSION

This study has found a very low incidence of venous thromboembolism (VTE) in Asian patients undergoing major hepatobiliary and pancreatic (HPB) surgery, similar to that of Western patients given chemoprophylaxis. In light of the low incidence of VTE in the Asian population, one must consider if the benefits of low molecular weight heparin (LMWH) does indeed outweigh the risks. The results of this study and that of the current literature available do not support the routine use of LMWH in Asians undergoing major HPB surgery.

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Author Contributions

B.C. Toh – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

T.C.Y. Pang – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

W.W.L. Woon – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

D.X.W. Yeo – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Y.Z. Lee – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

S.P. Junnarkar – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

J. K. Low – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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