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Incidence of bleeding in patients on different anticoagulants and antiplatelet therapies undergoing thoracentesis

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ABSTRACT

Introduction Thoracentesis is one of the most commonly performed procedures in the inpatient setting. Although coagulation profile is usually evaluated prior to thoracentesis, bleeding is a rare complication, occurring in less than 1% of the cases. Several society guidelines recommend holding antiplatelet medications and anticoagulants prior to thoracentesis. Clinical practice guidelines also recommend correcting international normalised ratios of more than two and platelet counts <50 X10^9/L.

Methods This is a retrospective descriptive study that included 292 patients who underwent thoracentesis in the inpatient setting at Ascension St John Hospital in Detroit, Michigan, USA from 2016 to 2018. We identified patients who had uncorrected risk for bleeding and collected data about their demographics, comorbidities, use of antiplatelet or anticoagulants and procedural details including complications. We looked for any postprocedural bleeding events to study their relation to the already established bleeding risk.

Results Two hundred and ninety-two thoracenteses were performed, 95.5% (n=279) were performed by interventional radiology. Majority of patients were at risk of bleeding 83% (n=242). No bleeding events occurred. Medications that were not held prior to thoracentesis included: clopidogrel 11% (n=32), novel anticoagulants 8.2% (n=24) and unfractionated heparin 50% (n=146). Use of ultrasound guidance decreased the amount of haemoglobin decline from 1 to 2 g/L (p=0.029). Seventeen patients suffered pneumothorax, eight of which required intervention.

Discussion Our study suggests that performing thoracentesis without correction of underlying coagulopathy may be safe. This may prevent consequences of holding essential medications and reduce the amount of blood products administered to patients in need of thoracentesis.

Key messages

- What is the incidence of bleeding complications in high-risk patients undergoing thoracentesis without proper correction of risk of bleeding?
- Bleeding complications were defined using the National Institutes of Health Common Terminology Criteria for Adverse Events V.4.03, 8 grades 2–5. There was no bleeding complications observed when thoracentesis was performed without correction of bleeding risk.
- We included a variety of patients in our study including patients receiving novel anticoagulants and double antiplatelet therapy. Holding such treatment for thoracentesis can sometimes result in major complications. In addition, in some cases, emergent thoracentesis is required in patients with severe respiratory distress to prevent intubation and mechanical ventilation.

INTRODUCTION

Thoracentesis is one of the most commonly performed procedures in the inpatient setting. In the USA, 132 472 thoracentesis procedures were performed on 99 509 patients between 2010 and 2013.[1] Although thoracentesis is considered to be a low bleeding risk procedure, platelet count and coagulation profile are usually evaluated prior to the procedure.[2–4] In addition, several society guidelines recommend holding antiplatelet medications such as clopidogrel and prasugrel for 5 days prior to the procedure as well as holding one dose of unfractionated heparin prior to thoracentesis.[5] Clinical practice guidelines also recommend correcting international normalised ratios (INRs) of more than two and platelet counts less than 50 X 10^9/L.[5] In a systematic review published in 2005, Segal and Dzik found insufficient evidence to conclude that abnormal coagulation panels predict bleeding in patients undergoing invasive procedures.[6] Other studies had demonstrated the safety of performing thoracentesis on patients taking clopidogrel.[4 7] At this time, there are no studies that identify the risk of bleeding in patients on novel anticoagulants (NOAC); however, it is generally recommended that these medications be held for at least 24 hours prior and after low

risk procedures such as thoracentesis.[8 9] This is often impractical and may cause a delay in diagnosis. In addition, patients with large effusions may suffer respiratory distress which may result in intubation if thoracentesis is not performed promptly. The primary objective of this study was to describe the risk of bleeding in adult patients who underwent thoracentesis. The secondary objective was to assess the risk of pneumothorax in patients who underwent thoracentesis.

METHODS

This is a retrospective chart review of patients admitted at Ascension St. John Hospital in Detroit, Michigan, USA between 1 January 2016 and 1 September 2018 who underwent thoracentesis during their hospital stay. Patients who presented for outpatient thoracentesis were excluded. Patients were identified by using the hospital billing database, patients with thoracentesis CPT codes 32 554 and 32 555 during the study period were included and a computer-generated random sample of 292 patients was selected. Electronic medical records (EMR) were reviewed for demographic data, comorbidities, medications, laboratory values, in-hospital setting (floor vs intensive care unit (ICU)) and the presence of invasive ventilation during thoracentesis. Different thoracentesis kits were used depending on the operator, typically six-French catheters were used. Patients were identified as having an increased risk of bleeding based on the following criteria:[10]

- Use of any antiplatelet medication such as clopidogrel, ticagrelor or prasugrel with or without aspirin within 5 days before the procedure.
- Use of any of the following direct oral anticoagulants: dabigatran, apixaban, rivaroxaban or edoxaban, within 3 days of the procedure.
- Use of warfarin with or without aspirin within 5 days before the procedure.
- Use of enoxaparin within 12 hours before the procedure.
- Use of unfractionated heparin within 4.5 hours before the procedure.
- INR greater than 1.5, because of either warfarin or liver disease without correction prior to thoracentesis.
- Platelet count less than 50 X10^9/L without correction prior to thoracentesis.
- Renal disease defined as creatinine greater than 1.5 mg/dL or patients requiring renal replacement therapy.

The half-life of NOAC depends on creatinine clearance with recommendations to hold NOAC for longer periods with worse kidney functions.[10] We, thus, decided to consider patients to be at risk of bleeding if NOAC were held for less than 3 days in order to standardise data collection and due to high prevalence of chronic kidney disease in our general patient population.

Patients were classified as having low risk of bleeding if transfused with platelets, fresh frozen plasma, cryoprecipitate or if they received vitamin K prior to thoracentesis. Patients were also classified as having low risk if any of the following medications were held 5 days prior to the thoracentesis: warfarin, clopidogrel, ticagrelor or prasugrel with or without aspirin. On the review of EMR, no special precautions were taken during the thoracentesis for patients at increased risk of bleeding. Extensive chart review was performed to include daily laboratory and radiologic data, progress notes following the thoracentesis to identify complications related to the procedure, blood transfusions following thoracentesis and attempts to correct coagulopathy prior to the procedure.

Bleeding complications were defined using the National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) V.4.03, 8 grades 2–5. A grade 2 haematoma refers to a haemorrhagic event requiring evacuation or aspiration; grade 3 requiring transfusion, radiologic, endoscopic or elective operative intervention; grade 4 requiring urgent intervention because of life-threatening consequences and grade 5 referring to a haemorrhagic event leading to death. Patient's EMR chart was reviewed from the day of the procedure until discharge for complications related to the procedure, including chest radiology and need for transfusion as well as need for chest tube insertion up to 3 days postprocedure.

Patient and public involvement

Given the nature of retrospective chart review, most of the patients were no longer receiving medical care at our hospital. Also, contact information to patients might have been unavailable. Based on the retrospective nature of the study, it was determined by the IRB that obtaining informed consent was not needed.

Statistical analysis

Continuous variables were reported as the mean with SD or median with range or IQR. Categorical variables were reported as frequency distributions. Comparison of bleeding by anticoagulant type was compared using Mann-Whitney test. Statistical analyses were performed using IBM SPSS Statistics for Windows, V.26 (IBM). A p value of 0.05 or less was used to indicate statistical significance.

RESULTS

Our study included 292 patients. Fifty-two per cent were females (n=152) and 47% were males (n=140). The majority of patients were white (67%, n=198) and 29% were black (n=85). The mean age was 70.6±14.1 years. Patients had multiple comorbidities including chronic kidney disease (42.8%), chronic obstructive pulmonary disease (32.5%) and haemodialysis-dependent renal failure (12.7%). Around one-third of patients were in the

Table 1 Patient characteristics

No of patients	292
Sex	
Female, n (%)	152 (51.7)
Male, n (%)	140 (46.9)
Race	
African American, n (%)	85 (29.1)
White, n (%)	198 (67.8)
Other, n (%)	9 (3)
Median age (range)	71 (28–98 years)
Comorbidities	
Chronic kidney disease, n (%)	125 (42.8)
Haemodialysis, n (%)	37 (12.7)
Mechanical ventilation, n (%)	44 (15.1)
Intensive care unit patient, n (%)	102 (34.9)
History of COPD, n (%)	95 (32.5)
Average INR (range)	1.3 (0.9–3.1)
Average platelet count (range)	238 X10^9/L (33X10^9/L–755X10^9/L)
Medications increasing risk of bleeding	
Unfractionated heparin, n (%)	146 (50%)
NOAC, n (%)	24 (8.2%)
Clopidogrel, n (%)	32 (11%)
Enoxaparin, n (%)	17 (5.8%)
Warfarin, n (%)	11 (3.8%)

COPD, chronic obstructive pulmonary disease; INR, international normalised ratios; NOAC, novel anticoagulants.

ICU (34.9%) and 15% were on mechanical ventilation. Table 1 summarises patients characteristics.

Half of the patients that were considered high risk for bleeding were receiving unfractionated heparin (50%) which is commonly used as in-patient deep vein thrombosis prophylaxis, while 11% were on clopidogrel and 8.2% used NOAC.

All patients underwent diagnostic and therapeutic thoracentesis. The majority of the thoracenteses were performed by the interventional radiology department (95.5%). Ultrasound guidance was used in most cases (96.2%) and the average amount of pleural fluid drained was 877.2±705 mL. Table 2 summarises procedural data.

There were no major bleeding complications (CTCAE grades 2–5), thus, we decided to look at drop of haemoglobin in patients who were at risk of bleeding. Haemoglobin levels were followed for up to 3 days following thoracentesis in patients at risk of bleeding. Haemoglobin decline was calculated by measuring preprocedural haemoglobin minus postprocedural haemoglobin with the lowest haemoglobin value within the next 3 days after thoracentesis being used as the value.

Table 2 Characteristics of procedural data

Thoracentesis indication	
Diagnostic and therapeutic, n (%)	292 (100)
Service performing thoracentesis	
Interventional radiology, n (%)	279 (95.5)
Pulmonology, n (%)	13 (4.5%)
Imaging	
Ultrasound guidance during thoracentesis, n (%)	281 (96.2)
Chest X rayX-ray following thoracentesis, n (%)	251 (86%)
Mean amount of pleural fluid drained (±SD)	877 mL (±705 mL)
Complications	
Rate of pneumothorax, n (%)	17 (5.8%)
Rate of haemothorax, n (%)	0
Rate of pneumothorax requiring chest tube intervention n (%)	8 (4.7%)

The rate of pneumothorax was 5.8% (n=17). Eighty-three per cent of patients were at risk of bleeding (n=242), however, only 1% (n=22) received correction of coagulopathy. In patients who were at risk of bleeding, 52.7% (n=116) experienced a decline in haemoglobin following up to 3 days following thoracentesis. Use of ultrasound guidance decreased the amount of haemoglobin decline from a median of 10 g/L (95% CI −0.28 to −0.05) to 2 g/L (95% CI −0.840 to −1.50) with p value of 0.03. However, these data may be skewed due to the limited number of patients who underwent thoracentesis without ultrasound guidance.

None of the medications that increased risk of bleeding caused a clinically significant drop in haemoglobin. The median decline in haemoglobin in patients on clopidogrel was4 g/L (95% CI −0.55 to 0.15) vs 2 g/L (95% CI −0.28 to −0.05) in patients who did not receive the medication (p=0.30) and the median decline in haemoglobin in patients who received NOACs was 2.5 g/L (95% CI −0.43 to −0.003) vs 2 g/L (95% CI −0.28 to −0.04) in those who did not receive them (p=0.86). Table 3 compares the median haemoglobin decline by medications. Haemoglobin decline was followed for 3 days following thoracentesis.

Patients in the ICU had a statistically significant increase in haemoglobin decline with a median of 4 g/L (95% CI −0.512 to −0.129) in comparison to patients on the floor with a median haemoglobin decline of 0.5 g/L (95% CI −0.214 to 0.055) with a p value of 0.03, however, the drop was not clinically significant and did not fulfil the criteria of CTCAE grades 2–5. Paradoxically, haemodialysis patients appeared to have less severe haemoglobin decline of 1 g/L (95% CI −0.210 to 0.564) in comparison to those who are not on haemodialysis with haemoglobin

Table 3 Comparison of median haemoglobin decline by medications

Medication		N (%)	Median haemoglobin decline (g/L) (95% CI)	P value
Clopidogrel	Administered	32 (11)	4 (–0.55 to 0.15)	0.30
	Not administered	260 (89)	2 (–0.28 to –0.05)	
Aspirin	Administered	74 (25)	2 (–0.33 to –0.007)	0.88
	Not administered	281 (75)	2 (–0.32 to –0.017)	
Unfractionated heparin	Administered	146 (50)	2 (–0.359 to –0.036)	0.73
	Not administered	146 (50)	2 (–0.293 to 0.011)	
Lovenox	Administered	17 (5.8)	4.5 (–0.862 to 0.719)	0.40
	Not administered	275 (94.2)	2(–0.280 to –0.060)	
Novel anticoagulant	Administered	24 (8.2)	2.5 (–0.43 to –0.003)	0.86
	Not administered	268 (91.8)	2 (–0.28 to –0.04)	
Warfarin	Administered	11 (3.8)	2 (–0.969 to 0.149)	0.58
	Not administered	281 (96.2)	2 (–0.270 to –0.042)	

decline of 2 g/L (95% CI −0.328 to −0.100) with a p value of 0.06. Table 4 compares median haemoglobin decline by comorbidities.

DISCUSSION

This retrospective study suggests that performing thoracentesis without correction of underlying coagulopathy, holding antiplatelets or anticoagulants may be safe as none of the patients had any bleeding events. This may prevent consequences of holding essential medications such as antiplatelets or anticoagulants and reduce the amount of transfusions administered to patients in need of thoracentesis. Our results are comparable to a study that evaluated correction of INR and platelet count in one group versus the second group that was not corrected.[11] The study showed no significant risk of bleeding in patients who underwent ultrasound guided thoracentesis with platelet counts <50X10^9/L or INR >1.6.

The majority of the thoracenteses that were evaluated in our study were performed by the interventional radiology department (95.5%), which may have played a role in the results. Unfractionated heparin was the most common medication used that increased the risk of bleeding (46.5%). Unfractionated heparin was not held appropriately prior to thoracentesis; however, median haemoglobin decline appeared to be equal in both groups of patients that received it vs those who did not, with a median haemoglobin decline of 2 g/L in both groups (p=0.73). Nevertheless, no bleeding incidents occurred. Alternately, the use of clopidogrel prior to thoracentesis had a median decline of haemoglobin of 4 g/L vs 2 g/L in patients who did not receive it (p=0.30). But overall, no bleeding incidents occurred. This is similar to studies done by Zalt *et al*, Perl *et al* and Mahmood *et al* which yielded similar results in safety of clopidogrel even in placement of small-bore chest tubes.[4 12 13] This is particularly important in patients with recent stent placement as premature discontinuation of clopidogrel is associated with increased risk of mortality.[14–16]

In addition, our rate of pneumothorax appears to be similar to reports in literature. In a meta-analysis that included over 6,000 thoracenteses, the rate of pneumothorax was 6% which is similar to our rate of pneumothorax of 5.8%.[17]

Limitations of retrospective studies are well known and may have affected some of our results. Patients on haemodialysis appeared to have less severe haemoglobin decline of 1 g/L in comparison to those who were not on haemodialysis with haemoglobin decline of 2 g/L and p value of 0.06. This maybe confounded by our inability to accurately detect

Table 4 Comparison of median haemoglobin decline by comorbidities

Comorbidity		N (%)	Median haemoglobin decline (g/L)	P value
COPD	Yes	95 (32.5)	1.5	0.244
	No	197 (67.5)	2.5	
ICU	Yes	102 (34.9)	4	0.03
	No	190 (65.1)	0.5	
Mechanical ventilation	Yes	44 (15.1)	3.5	0.237
	No	248 (84.9)	2	
Haemodialysis	Yes	37 (12.7)	1	0.056
	No	255 (83.3)	2	

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

blood transfusions via retrospective chart review. This may also explain why patients on NOAC appeared to have not lost any blood in comparison to those not receiving NOACs with median haemoglobin decline of 0 g/L vs 2 g/L. Nevertheless, in both patient groups no major intrapleural haemorrhage that fulfil CTCAE occurred as charts were thoroughly reviewed for such complications.

In conclusion, this is yet another study that shows low risk of bleeding associated with thoracentesis. Level of comfort for the operator as well as the overall clinical scenario will play major roles in determining benefit versus risk of performing thoracentesis in patients at risk of bleeding.

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