The Safety of Thoracentesis in Patients with Uncorrected Bleeding Risk

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Abstract

Background: Thoracentesis is commonly performed to evaluate pleural effusions. Many medications (warfarin, heparin, clopidogrel) or physiological factors (elevated International Normalized Ratio [INR], thrombocytopenia, uremia) increase the risk for bleeding. Frequently these medications are withheld or transfusions are performed to normalize physiological parameters before a procedure. The safety of performing thoracentesis without correction of these bleeding risks has not been prospectively evaluated.

Methods: This prospective observational cohort study enrolled 312 patients who underwent thoracentesis. All patients were evaluated for the presence of risk factors for bleeding. Hematocrit levels were obtained pre- and postprocedure, and the occurrence of postprocedural hemothorax was evaluated.

Measurements and Main Results: Thoracenteses were performed in 312 patients, 42% of whom had a risk for bleeding. Elevated INR, secondary to liver disease or warfarin, and renal disease were the two most common etiologies for bleeding risk, although many patients had multiple potential bleeding risks. There was no significant difference in pre- and postprocedural hematocrit levels in patients with a bleeding risk when compared with patients with no bleeding risk. No patient developed a hemothorax as a result of the thoracentesis.

Conclusions: This single-center, observational study suggests that thoracentesis may be safely performed without prior correction of coagulopathy, thrombocytopenia, or medication-induced bleeding risk. This may reduce the morbidity associated with transfusions or withholding of medications.

Keywords: pleural effusion; pleural cavity; thoracentesis; coagulopathy

(Received in original form October 16, 2012; accepted in final form March 17, 2013)

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Supported by the National Institute on Aging through the Claude D. Pepper Older Americans Independence Center (P30AG21342) at Yale University (K.L.B.A. and T.E.M.).

Author Contributions: Conception and design: J.T.P., A.C.A., and M.A.P.; analysis and interpretation: J.T.P., A.C.A., T.E.M., and K.L.B.A.; drafting of manuscript and important intellectual content: J.T.P., A.C.A., M.A.P., and T.E.M.

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Ann Am Thorac Soc Vol 10, No 4, pp 336–341, Aug 2013

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DOI: 10.1513/AnnalsATS.201210-088OC

Internet address: www.atsjournals.org

Pleural effusions result from a vast array of medical conditions and prompt at least 173,000 thoracenteses each year in the United States (1). Many factors impact complication rates, including the use of ultrasound, operator experience, the use of manometry, and the number of attempts made to perform the procedure (1–6). Pneumothorax is the most common complication requiring intervention, and hemothoraces rarely occur (7).

Despite the infrequent occurrence of hemothorax, many institutional and society guidelines recommend correcting an International Normalized Ratio (INR) to less than 1.5 or 2.0, transfusing platelets to more than 50,000/ μ l, or withholding medications such as warfarin or clopidogrel before performing minimally invasive procedures including thoracentesis (8–12). In this single-center, observational study we prospectively evaluate the complications associated with thoracentesis in patients

with identified bleeding risks who did not receive preprocedural correction.

Methods

We conducted a prospective observational cohort study of patients undergoing thoracentesis by our pulmonary and critical care department between December 2010 and December 2011. Yale-New Haven Hospital (New Haven, CT) is a 1,000-bed

tertiary care center serving both the local New Haven community as well as a large referral base. All thoracenteses were performed by a physician or a physician assistant using ultrasound guidance. Approval for this study was obtained from the Yale University Institutional Review Board. Patients were included if they were age 18 years or older, required a thoracentesis for a pleural effusion, and provided informed consent.

Ultrasound (S-ICU; SonoSite, Bothell, WA) was used to identify the effusion. The procedure was typically performed with the patient sitting upright and leaning over a table. In those patients unable to sit upright, the head of the bed was elevated to 45 degrees and the thoracentesis was performed from a lateral position. A Safe-T-Centesis kit (Cardinal Health, Dublin, OH) was used after chlorhexidine antiseptis. A 6.0 French catheter was inserted with a needle into the pleural space and on fluid return, the needle was retracted and a pig-tail catheter was advanced. Pleural fluid was removed by manual aspiration until it no longer returned. Pleural fluid specimens were routinely evaluated for cell count, protein, lactate dehydrogenase, pH, cultures, and cytology. When bilateral effusions were present, both hemithoraces were aspirated simultaneously without a chest X-ray between procedures, as we have previously described and demonstrated to be safe (13).

Our definition of bleeding risk included the use of clopidogrel, therapeutic unfractionated intravenous heparin, or low molecular weight subcutaneous heparin (LMWH); an International Normalized Ratio (INR) greater than 1.5, due to either warfarin or liver disease; a platelet count less than 50,000/ μ L; or renal disease (defined as creatinine greater than 1.5 mg/dL or requiring renal replacement therapy). A patient with more than one risk factor for bleeding was placed into one category for analysis purposes, based on the following hierarchy: platelets less than 50,000/ μ L, INR greater than 1.5, use of clopidogrel, use of therapeutic LMWH or unfractionated heparin, and renal disease. If a patient had been transfused at the discretion of the primary physician immediately before performing the thoracentesis for an elevated INR or thrombocytopenia, they were classified as not having a bleeding risk. Similarly, if medications were withheld (clopidogrel for 7 d, warfarin for 5 d, heparin infusion for greater than 4.5 h, or

LMWH injection for greater than 12 h), these patients were included in the no-bleeding risk group. Aspirin use was not analyzed as its discontinuation is not necessary for thoracentesis (14). When consulted to perform a thoracentesis, we did not require reversal of laboratory abnormalities that are typically associated with bleeding risks.

To assess for procedure-related bleeding of significance, hematocrit determination pre- and 1 day postprocedure, requirement for blood product transfusions, chest radiograph abnormalities, hemothoraces, and death were recorded. All patients who had a thoracentesis performed had their clinical status evaluated 1 day postprocedure. A hematocrit decrease greater than 6% in the presence of a chest X-ray indicating an enlarging pleural effusion, hemodynamic instability, or death were criteria for development of a hemothorax. The mean change in hematocrit from baseline to Day 1 postprocedure was recorded. All patients underwent a follow-up interview at 1 month and there were no reports of bleeding or adverse events.

Statistical Analysis

Descriptive statistics were calculated and compared between patients with and without bleeding risk. The corresponding *P* values were from the Student *t* statistic for continuous variables and from the chi-squared statistic for dichotomous indicators. The mean changes in hematocrit from baseline to 1 day postprocedure between patients with and without bleeding risk were compared with a *t* test. After confirming that change in hematocrit was normally distributed, we proceeded to use ordinary least-squares regression to model this as a function of platelet count, INR, and creatinine. Two models were run. The first used continuous forms of all explanatory variables and the second used dichotomous forms of the same. Each model also included indicators for use of heparin and for persons reclassified as not at risk for bleeding subsequent to receiving a transfusion to correct their coagulopathy. Fifty-eight persons missed the 1-day postprocedure measure of hematocrit. Because most of the persons missing the second measure of hematocrit were treated as outpatients, and were therefore typically healthier than patients admitted to hospital, they cannot be assumed to be missing at random. For this

reason their data were not included and a complete case analysis was performed. Model fit was evaluated by residual analysis. All analyses were performed with SAS (version 9.2; SAS Institute, Cary, NC), and a *P* value less than 0.05 (two-tailed) was used to indicate statistical significance.

Results

A total of 312 unique patients were enrolled into this study; patient characteristics are shown in Table 1. Sixty-two patients underwent bilateral thoracentesis as requested during consultation for the procedure and as determined to be clinically indicated. This was typically for therapeutic purposes. Forty-two percent of our patient population (*n* = 130) had an increased risk of bleeding based on our *a priori* definitions. There was no significant difference in baseline demographics between patients with and without a bleeding risk factor (Table 1). The primary etiology of bleeding risk for our patient population is presented in Table 2. Elevated INR and renal disease were the two most common etiologies for bleeding risk. Of the 130 patients with a bleeding risk factor, 95 (73%) had one risk factor, 31 (24%) had two, and 4 (3%) had three, as shown in Figure 1. Sixteen patients had thrombocytopenia: 7 had only thrombocytopenia as their risk factor and 9 patients had one or more other risk factors. Fifty-one patients had an elevated INR: 25 had an isolated elevation in their INR and 26 had one or more other risk factors. Eighteen patients (14%) were taking clopidogrel: 10 were receiving clopidogrel alone and 8 had one or more other risk factors. Seventeen patients were receiving therapeutic LMWH or unfractionated heparin: 12 were receiving only heparin and 5 had one or more other risk factors. Sixty-seven patients had renal disease: 41 had renal disease as their only risk factor, and 26 had one or more bleeding risk factors. Eight patients in the bleeding risk group and 50 patients in the no-bleeding risk group were excluded from the outcome analysis because they were missing the postprocedure hematocrit, mostly because the thoracentesis was performed in the outpatient setting.

The pre- and postprocedural hematocrit levels between patients with and without bleeding risk were not significantly different.

Table 1. Comparison of patient characteristics on the basis of bleeding risk type

Patient Characteristic*	No Bleeding Risk (n = 182)	Bleeding Risk (n = 130)	P Value†
Age (yr), mean (SD)	66.7 (15.1)	68.6 (13.3)	0.2
Female, n (%)	95 (52)	60 (46)	0.3
Nonwhite race, n (%)	30 (17)	20 (16)	0.9
BMI (kg/in ²), mean (SD)	25.5 (6.8)	26.9 (7.0)	0.1
BMI > 30, n (%)	34 (19)	30 (23)	0.4
Ventilatory support, n (%)	15 (8)	11 (8)	0.9
Thoracentesis, unilateral, n (%)	151 (83)	99 (76)	0.1
Thoracentesis, bilateral, n (%)	31 (17)	31 (24)	0.1

Definition of abbreviation: BMI = body mass index.

Ventilatory support included mechanical ventilation, continuous positive airway pressure, and bilevel positive airway pressure.

*Total number of patients: 312.

†P values were calculated from the Student *t* statistic for continuous variables and from the chi-squared statistic for dichotomous variables.

In the model with continuous predictors of platelet count, INR, and creatinine, none of these terms showed a statistically significant association with mean change in pre- versus postprocedural hematocrit levels. In the model with dichotomous predictors of platelet count, INR, and creatinine, the indicator for INR was marginally associated with a *P* value of 0.04 with a coefficient of −0.89, indicating that for each unit rise in INR, the change in hematocrit would decrease by approximately 0.9. A sensitivity analysis of each of these models was also run wherein the four participants with platelets less than 20,000/μl and the five participants with INR greater than 3 were excluded, resulting in negligible changes in coefficient values and their corresponding *P* values.

Two patients had a significant drop in hematocrit of 6.1 and 8.1. The medical records were reviewed to assess for a procedural complication to explain this decline. The first patient was receiving an unfractionated heparin drip for an upper extremity thrombosis. She had no sign of active bleeding and her hematocrit was back to baseline without a transfusion several hours later, suggesting a laboratory error. The second patient underwent thoracotomy with decortication after thoracentesis for an empyema where he bled 300 ml intraoperatively and received 4 units of fresh frozen plasma and 3 L of intravenous fluids intraoperatively, suggesting a combination of operative blood loss and dilution from intravenous fluids as the etiology. No patients developed a hemothorax and there were no deaths related to the procedure. Table 3 presents a comparison of the mean change in hematocrit between those with and without bleeding risk. These mean changes between those with and without

bleeding risk are not significantly different. Table 4 focuses only on those with bleeding risk and provides the mean change in hematocrit among the five attributed etiologies. Because each etiological subtype has a small sample, they each have high values of standard deviation. These large standard deviations reflect large dispersion and highly overlapping confidence levels, meaning they are not significantly different. This is likely a matter of insufficient power to detect such differences. Figure 2 presents box plots of the pre- versus postprocedural hematocrit values for patients with and without bleeding risk. At follow-up interviews 1 month postprocedure, including patients missing the postprocedural measure of hematocrit, there were no reports of bleeding or other adverse events related to the thoracentesis.

Discussion

This single-center, observational study of 312 patients undergoing thoracentesis, 130 (42%) of whom had a bleeding risk, suggests

that the procedure may be safe to perform in patients with elevated INR, patients with thrombocytopenia, and patients receiving anticoagulants such as warfarin, heparin, and clopidogrel. This study not only highlights the prevalence of patients with a bleeding risk, but is also the first prospective series examining the safety of the procedure in patients with a variety of uncorrected bleeding risks. Patients who had a bleeding risk that was corrected by transfusion or by withholding of medication were not included in our bleeding risk group. Other studies addressing this question are limited to retrospective analysis (15), a study of 30 patients taking clopidogrel (16), or consensus statements that admit a lack of current data (14). The most recent consensus statement on percutaneous procedures acknowledges the paucity of data regarding periprocedural management of patients with abnormal coagulation factors, and cites references that can neither “recommend nor refute” prophylactic transfusions. Furthermore, these guidelines state that coagulation times should not be assumed to represent an

Table 2. Proportional distribution of bleeding risk subtypes

Subtype of Bleeding Risk* (n = 130)	n (%)
Thrombocytopenia, platelets < 50,000/μl	16 (12)
INR > 1.5 secondary to liver disease or warfarin therapy	44 (34)
Clopidogrel	15 (12)
Therapeutic low molecular weight heparin within 12 h or therapeutic unfractionated heparin within 4.5 h of procedure	14 (11)
Renal disease, creatinine > 1.5, or receiving renal replacement therapy	41 (31)

Definition of abbreviation: INR = International Normalized Ratio.

*Although patients may have had more than one bleeding risk factor they were categorized into one type of bleeding risk group as described in METHODS.

Figure 1. Bleeding risk categories (n = 130). Patients who underwent thoracentesis had between one and three risk factors for bleeding, as shown. INR = International Normalized Ratio.

increased risk for periprocedural bleeding or used as an indication for transfusion (14). Despite this, physicians are reluctant to perform thoracentesis on patients with bleeding risks without correction of coagulopathy. Barriers to advancing our understanding of risks for bleeding in these situations include the risk of causing a complication and harming the patient, as well as legal ramifications. To make informed medical decisions one needs to balance the iatrogenic risks of transfusion or the stopping of medication against the potential benefits.

The number of patients in clinical practice with a bleeding tendency, as defined by our group, is significant. In our cohort, 42% of patients in whom a thoracentesis was performed had a bleeding risk. Using the aforementioned estimate that 173,000 thoracenteses are performed annually in the United States, physicians here must decide about correcting bleeding parameters in approximately 72,660 patients each year before performing thoracentesis. Using current clinical recommendations, this large number of patients is currently at risk for transfusion-related reaction due to blood products or the risks related to withholding of anticoagulant medications.

Transfusions are the most common procedure performed in the hospital. The costs and risks of transfusion are substantial. Approximately 3 million units of fresh frozen plasma (17), 9 million units of

platelets (8, 18, 19), and 14 million units of packed red blood cells (pRBCs) (19, 20) are transfused every year in the United States. Morbidity associated with transfusion is not uncommon (10, 20). Acute lung injury can lead to respiratory failure, mechanical ventilation, prolonged hospitalization, profound long-term morbidity, or even death. The risk of transfusion-related acute lung injury is estimated at 1 in 2,000–4,000 units (21). In addition to respiratory failure, multisystem organ failure due to anaphylaxis or hemolysis may occur. Anaphylaxis occurs in 1 of 30,000 transfusions and acute hemolysis in 1 of 50,000. Although less than in the past, there is still some risk for life-long debilitating infections such as HIV or hepatitis B or C. There is growing evidence that repeated transfusions may have adverse immunologic consequences as well. Transfused red blood cells, platelets, or coagulation factors can induce alloantibodies. Once formed, these

alloantibodies may be a barrier to future transfusions or even transplantation. The rate of alloimmunization to pRBCs is 3–5% and alloimmunization to platelet antigens is approximately 8% (22). These risks of direct complications do not account for the significant financial burden associated with the use of blood products or the depletion of available blood products, making them unavailable for life-threatening conditions.

Despite the recommendations for correcting bleeding risks, to our knowledge there are no studies prospectively evaluating bleeding due to thoracentesis. McVay and Toy in 1991 published a retrospective review of paracentesis and thoracentesis performed without correction of abnormal clotting parameters (23); specifically the prothrombin time, INR, partial thromboplastin time, and platelet counts. Similar to our study, no patient who underwent thoracentesis experienced a bleeding complication. Patel and Joshi published another retrospective study in 2011, in which they reported on 1,076 thoracenteses performed under ultrasound guidance by interventional radiologists (15). Of 1,076 procedures, 497 were performed on patients who had an INR greater than 1.5 (range, 0.91–6.19), and 123 had a platelet count less than 50,000/ μ l (range, 9,000–49,000/ μ l, including 12 patients with platelet counts less than 25,000/ μ l). They also found no hemorrhagic complications related to the procedure in any patient (15). Finally, 30 patients in a prospective study underwent thoracentesis while taking clopidogrel without complications (16). There are no other published studies to our knowledge that address this issue. As such, we propose that our prospective analysis may significantly inform current practice.

The risk of hemothorax due to thoracentesis is low (<1% [24]), even in critically ill patients (0.6% [7]). In the meta-

TABLE 3. Mean change in hematocrit by bleeding risk of patients

Bleeding Risk Type (n = 254)*	n (%)	Change in Hematocrit Mean (SD)
No bleeding risk	132 (52)	−0.2 (2.4)
Bleeding risk	122 (48)	−0.5 (2.9) [†]

*Of 312 participants, hematocrit levels for 254 were obtained both pre- and postprocedure. Fifty-eight participants were missing hematocrit data, typically because they were outpatients.

[†]Comparing patients with and without bleeding risk: *t* test *P* value = 0.4.

Table 4. Change in hematocrit by bleeding risk etiology

Attributed Etiology of Bleeding Risk (n = 122)	n (%)	Change in Hematocrit Mean (SD)
Thrombocytopenia, platelets < 50,000/ μ l	15 (12)	-0.7 (2.9)
Liver disease or warfarin, INR > 1.5	42 (34)	-1.1 (2.2)
Renal disease	37 (30)	0.3 (3.3)
Clopidogrel	14 (12)	-0.6 (3.4)
Therapeutic low molecular weight heparin within 12 h or therapeutic unfractionated heparin within 4.5 h	14 (12)	-0.9 (2.4)

Definition of abbreviation: INR = International Normalized Ratio.

analysis by Gordon and colleagues, there were 6 cases reported among the 6,605 thoracenteses, a rate of 1 in 1,000 (4). Comparing these data with the data of Patel and Joshi, there is no difference in the risk of hemothorax between the current algorithm for performing thoracentesis (after correcting bleeding parameters or holding medications) and performing the procedure in coagulopathic or thrombocytopenic patients.

Data from the surgical literature support our conclusions about the safety of continuing clopidogrel during thoracic procedures. Cerfolio and colleagues were the first group to report on the safety of general thoracic surgery for patients taking clopidogrel (25). Ceppa and colleagues demonstrated that patients undergoing major lung resection could also safely continue the medication preoperatively without a risk for increased bleeding (26). Notably, during surgical procedures, other resources such as electrocautery are available to stop bleeding if it occurs. The 18 patients in our study who underwent thoracentesis while taking clopidogrel had no bleeding or other adverse outcome. Of the 18 patients taking clopidogrel, 8 also had another bleeding risk factor including elevated INR, treatment with heparin, or renal disease. It is often impractical to wait 7 days before performing a thoracentesis while withholding clopidogrel, and the risks associated with platelet transfusion may be even greater for these patients.

It should be noted that our study population included patients who underwent bilateral thoracentesis, patients requiring ventilatory support, and others whose obesity sometimes made the identification of landmarks more difficult. Fifty percent of the patients who had a simultaneous bilateral thoracentesis met criteria for having a bleeding risk. Also, 26 of 312 participants (8%) were on ventilatory

support including mechanical ventilation, continuous positive airway pressure, and bilevel positive airway pressure. Sixty-four percent of our participants had a BMI greater than 30 and of these, 30 (47%) had a bleeding tendency. Despite these increased risks, none of these patients exhibited evidence of hemothorax.

There are several notable limitations of our study that warrant comment. First, this is a single-center observational study with a small group of practitioners trained in thoracentesis. The lack of randomization implies the possibility of bias due to an imbalance of unmeasured covariates. Second, because bleeding risk was evaluated only among patients referred for thoracentesis, there is an inherent selection bias in our sample. For example, we do not know whether the physicians referring patients for thoracenteses were screening out persons with notably high risk for bleeding. If that was the case, then our sample represents a group of persons with

lower risk of bleeding than may be seen in a wider selection of practices and hospitals. It is also possible that attending physicians referred only those patients who were expected to receive clinical benefit from the procedure. Another limitation of our study was a lack of direct observation for local hematomas, which prevented us from ascertaining whether patients with increased bleeding risk may have experienced localized bleeding. The inherent variability in hematocrit measurement is also a limitation, given that changes may reflect various conditions, including volume resuscitation, repeated blood draws, or bleeding elsewhere. However, no patients had a significant drop in hematocrit that was not readily explained, and no patient experienced a sizable effusion within 24 hours of the procedure that would be consistent with hemothorax. Furthermore, no patient had hypotension or subsequent evacuation of the pleural space due to hemothorax. In terms of missing data, we

Figure 2. The median change in hematocrit (%) in patients with and without a risk for bleeding during thoracentesis (n = 254).

had 58 participants who did not have a postprocedural hematocrit check because their procedures were performed on an outpatient basis. For this reason we might have missed bleeding that occurred postprocedure. However, even for these 58 participants without postprocedural hematocrit values, all patients in our sample were interviewed 1 day postprocedure and none reported any complications.

This is a single-center examination of mostly inpatients with routine use of ultrasound-guided thoracentesis. Although one expert physician was responsible for most procedural oversight, many of the

procedures were performed by residents and fellows in training. Because our procedures were performed in a general medical population, we believe these results are reflective of the wide range of patients commonly encountered in clinical practice.

Conclusions

Thoracentesis is a mainstay for diagnosing and treating pleural effusions. Certain safety measures are important, including appropriate antisepsis, the use of ultrasound guidance, and needle insertion laterally above the rib. We assert that the preemptive

correction of bleeding parameters or withholding of medication may create safety issues of their own. This study suggests that thoracentesis may be safely performed in the majority of patients with coagulopathy, thrombocytopenia, or medication-induced bleeding risk without prior correction. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgments: The authors thank Anna Kookoolis, M.A., for assistance with data collection, and Kelsey Johnson, P.A., for diligent care of patients.

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