EBUS-TBNA and EUS-FNA

Risk Assessment for Patients Receiving Clopidogrel

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Background: **Clopidogrel is widely used for the prevention of thrombotic vascular complications. Its primary potential toxicity is bleeding. Management of clopidogrel therapy for patients undergoing invasive procedures is an area of ongoing study. We sought to evaluate the bleeding risk for patients undergoing needle aspiration biopsy by endobronchial ultrasound (EBUS) or esophageal ultrasound (EUS) while taking clopidogrel.**

Methods: **Retrospective review of sequential cases of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and esophageal ultrasound fine needle aspiration (EUS-FNA).**

Results: **Three hundred ninety-five consecutive procedures were reviewed. Thirty-seven patients were taking clopidogrel at time of biopsy. The patients taking clopidogrel were significantly older than those in the control group. Two patients (1%) in the control group were admitted for observation, but neither was found to have a significant bleed. There were no clinically significant bleeding complications in either of the study groups.**

Conclusions: **It is reasonable to proceed with EBUS-TBNA or EUS-FNA when both, (1) clopidogrel cannot be stopped and, (2) an important diagnostic question is at stake.**

Key Words: clopidogrel, endobronchial ultrasound, bleeding, esophageal ultrasound

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Clopidogrel and its congeners are widely used in patients with cardiovascular disease and are considered mandatory after some endovascular procedures, with a high risk of vascular reocclusion if not taken.[1] Patients taking clopidogrel may need to undergo invasive procedures. The literature regarding the risk (primarily bleeding) for procedures performed upon patients receiving clopidogrel is incomplete. One area inadequately addressed to date is that of the safety profile of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and esophageal ultrasound fine needle aspiration (EUS-FNA) in patients currently taking clopidogrel. This report is a retrospective review of the safety/complication profile of endoscopic needle aspiration procedures performed on patients for whom biopsy was felt to be important but for whom clopidogrel could not be stopped.

METHODS

The Institutional Review Board was petitioned and granted consent (University of Arkansas for Medical Sciences protocol #204048) for a retrospective chart review of consecutive EBUS-TBNA and EUS-FNA procedures performed by interventional pulmonary staff at 1 institution between July 31, 2014 and June 30, 2015. All procedures were performed in the bronchoscopy suite under conscious sedation in the form of physician-administered propofol. All patients were supine with head elevation of ~30 degrees, and no repositioning was performed regardless of whether EBUS, EUS, or a combined procedure was performed. All EBUS-TBNA and EUS-FNA procedures were performed orally through a bite block; there was no intubation or use of an laryngeal mask airway. All procedures were performed with a convex curvilinear bronchoscope (Olympus UC180F). A 22-G needle (Olympus Medical Systems Corp., Tokyo, Japan) was used for all procedures. We

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did not use Doppler during nodal sampling. Suction was routinely applied in all cases. Rapid on-site cytologic examination (ROSE) was available for all procedures. The following data were collected: age, sex, procedure, number of sites biopsied during the procedure, whether or not the patient was receiving antiplatelet drugs or anticoagulants, procedure-related bleeding, hemoglobin preprocedure and postprocedure when available, required interventions related to complications, and additional procedures performed during the same sedation. Patients who had been taking clopidogrel but had held it for more than 4 days before the procedure were put in the control group. Patients receiving aspirin as their only antiplatelet therapy were not included in the antiplatelet group. For purposes of this study, bleeding was considered significant if there was a drop in hemoglobin of 2 or more g/dL or if there was any acute or delayed bleeding that per se required observation or intervention. All patients undergoing EBUS-TBNA and/or EUS-FNA during the study interval were included in initial analysis. Data were analyzed using SPSS.

RESULTS

Global results are delineated in Table 1. Three hundred and ninety-five consecutive cases were reviewed, with preprocedure and postprocedure hemoglobin available for 211 of them. There were 198 EBUS-TBNA cases and 197 EUS-FNA cases. Seventy-eight of these procedures involved performance of both EBUS-TBNA and EUS-FNA. In 25 of these, EBUS-TBNA was performed first, and for the remaining 53, EUS-FNA was performed first. Each of these is placed under the category of the first procedure performed, and all 395 procedures were pooled for result analysis. Seven patients had been taking clopidogrel but had stopped it more than 4 days before their diagnostic procedure and were therefore put in the control group. The study group comprised 37 patients who had continued clopidogrel periprocedurally. Thirty-one of the 37 patients had undergone coronary angiography with drug-eluting cardiac stent insertion 16 ± 8 days before endoscopic biopsy, with cardiology feeling that the risks of cessation of clopidogrel were unacceptable. Suspect abnormalities had been found in the process of work-up or treatment of coronary artery disease, and stenting had not been held because of the abnormalities. The remaining 6 patients had undergone drug-eluting stent insertion 91 ± 27 days before endoscopic biopsy. We would have been comfortable with brief cessation of clopidogrel therapy for these 6, but the patients insisted that we proceed while they continued clopidogral after being informed of the increased risk of bleeding. No other antiplatelet agents (excluding aspirin, as noted) had been prescribed. Twenty of the patients receiving clopidogrel underwent EUS-FNA, and 17 underwent EBUS-TBNA. The remaining 358 patients served as the control group.

There was a significant difference between groups in age, with an older mean age for patients receiving clopidogrel. There was also a significant difference in additional procedures,

TABLE 1. Study Cases

	Antiplatelet Therapy	No Antiplatelet Therapy	*P* (When Relevant)
No. patients	37	358	
Sites biopsied	83	951	
Sex (male/female)	22/15	200/158	
Age	69 ± 23	58 ± 18	< 0.0001
Biopsy sites	2.3 ± 1.9	2.6 ± 2.1	0.97
Aspirations/site	3.87 ± 2.78	5.12 ± 3.96	0.078
Added procedures [n (%)]	7 (19)	87 (24)	< 0.0002
Complications	0	2	0.652
Interventions	0	1	
ΔHgb (g/dL)*	1.1 ± 2.9	1.3 ± 1.7	0.69

*ΔHgb indicates hemoglobin before FNA versus procedure after FNA, when available (n = 211 for this row only).

TABLE 2. Specific Sites Biopsied by EBUS-TBNA and EUS-FNA for Patients Receiving Antiplatelet Therapy

	EBUS	EUS	Total
2L		3	3
4L		18	18
4R	7		7
7		12	12
8		3	3
9		2	2
11L	7		7
11R	9		9
12R	1		1
LAD		4	4
Mass	4	13	17
Total	28	55	83

EBUS-TBNA indicates endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA, esophageal ultrasound fine needle aspiration; LAD, left adrenalL, left; R, right.

with more patients in the control group undergoing additional procedures. Procedures in the control group consisted of thoracentesis, transbronchial lung biopsy, and minor ablative procedures. In the study group, there was 1 electocautery snare of an endobronchial lesion and there were 6 thoracenteses. For the 358 control patients, 951 sites were sampled with EBUS-TBNA and/or EUS-FNA. Seventeen of the sites (1.7%) had been deemed inadequate at time of ROSE, but after cell block analysis all 951 were reported as adequate. For the 37 patients in the clopidogrel group, 83 sites were sampled with EBUS-TBNA and/or EUS-FNA. One (1.2%) had been deemed inadequate at time of ROSE, but after cell block analysis it was reported as adequate. The number of needle passes per site was 5.12 ± 3.96 for the control group and 3.87 ± 2.78 for the clopidogrel group ($P = 0.078$). The breakdown of sampling by EBUS-TBNA versus EUS-FNA is delineated in Table 2.

Final diagnoses for the study patients are presented in Table 3. Overall, 46 of the 83 sites sampled in the clopidogrel group (55%) contained malignant tissue. The majority of these were lung cancers, with 3 esophageal cancers, 1 choriocarcinoma, and 1 lymphoma.

There were no instances of significant bleeding in either group. There were 2 complications in the control group, neither of which was a significant bleed. The first of these 2 patients had some bleeding in mediastinal tissues seen by ultrasound in the area of nodal biopsy, raising concern for a clinically relevant bleed. There had been no abnormal bleeding into the airway. She was admitted for observation after EBUS-TBNA and underwent a computed tomography angiogram, with no evidence of active bleeding on that study. Her hemoglobin had been 11.2 before the procedure and was 10.3 the next morning, when she was discharged; significant bleed had been ruled out, and she had been clinically stable throughout. The second patient presented 3 days after an EBUS-TBNA of station 11R with dyspnea and chest pain. Radiography demonstrated a right pleural effusion. A chest tube was inserted, revealing a blood-tinged exudative effusion. It was not a hemothorax, and no transfusion was required. The pathogenesis of this process was unexplained, but the effusion was temporally related to the EBUS-TBNA procedure; although significant bleeding did not occur, it did appear to

TABLE 3. Final Diagnoses for Patients Receiving Antiplatelet Therapy

	Total	2L	4L	4R	7	8	9	11L	11R	12R	LAD	Mass
Small cell*	4	1	1								1	1
AdenoCa*	17		4		2	1			1		2	7
Sq Cell Ca*	20		9		5							6
Granulomas	14		4	1	4			1	1			3
Carcinoid	1									1		
Esophageal Ca*	3					2	1					
Choriocarcinoma	1						1					
Lymphoma	1			1								
Benign adequate	22	2		5	1			6	7		1	

*Final typing and origin (lung vs. esophagus) determined by immunohistochemistry.
AdenoCa indicates adenocarcinoma; LAD, left adrenal; Sq cell Ca, squamous cell carcinoma.

be a complication that was related to the procedure and that required intervention.

DISCUSSION

Drugs that inhibit adenosine diphosphate-mediated platelet aggregation are a mainstay of the therapy of cardiovascular disease, and are now considered an essential adjunct to the placement of drug-eluting cardiac stents.[2–8] Several drugs in this class have been developed[1,9]; at present, clopidogrel is the most widely used. Clopidogrel was the only adenosine diphosphate receptor inhibitor prescribed to patients in this study. Transbronchial biopsy of patients taking clopidogrel has been shown to be prohibitively dangerous,[10] whereas it has now been shown that patients taking clopidogrel can undergo percutaneous dilational tracheostomy, ultrasound-guided chest tube insertion, polypectomy, and percutaneous gastrotomy with far lower risk than that incurred with transbronchial lung biopsy.[11–15] In this retrospective review, we have shown a low risk of complications for patients undergoing endosonographic FNA. None of patients in either study group experienced significant bleeding. There were no complications in the clopidogrel group, as opposed to 2 clinically relevant complications among the 358 control patients (P = NS).

We are aware of 2 small case series related to this specific issue. Stather et al[16] retrospectively reported 12 cases of patients who underwent EBUS while on clopidogrel. There were no cases of clinically significant bleeding in their series. An article by Trindade et al[17] has just been published. The authors noted no clinically relevant bleeding associated with 10 EUS-FNA procedures. Our series is more extensive than either of these, and included both EBUS-TBNA and EUS-FNA. We would argue that the collective negative (59 cases from 3 consecutive series with no significant bleeding) is more important than the results of any study alone.

We interpret these results with caution. Antiplatelet therapy will increase the severity of bleeding when it does occur, and we do not condone unnecessary risk. Clinically relevant complications did occur in 0.5% of our overall study population, and had either of these patients been receiving antiplatelet therapy the complications may have been more severe. Just as we do for percutaneous tracheostomy and chest tube insertion, we advocate cessation when possible of any therapy that could lead to an increase in procedure-associated bleeding.[11–13] This study did not demonstrate an increased risk of bleeding for either route of access (airway or esophagus), and we have no reason to suspect that 1 route would be less likely to cause bleeding than the other. We do nevertheless assume that bleeding will eventually complicate one of our procedures and that the bleeding into the esophagus will cause less compromise than bleeding into the airways. For this reason, we elected in this study to use the esophagus as the route of access whenever either route would allow us to answer the clinical question at hand.

This study is limited. It is retrospective. The number of patients receiving clopidogrel was relatively low; had the number been larger, additional cases of bleeding may have occurred. The results cannot be extrapolated to other members of the same drug class, as each has different degrees of platelet inhibition and different bleeding risks.[1] The study results cannot be applied to other disease-related or drug-induced coagulopathy. The study was not blinded, and the knowledge that a patient was receiving clopidogrel could have led to changes in performance such as the limitation of trainee participation. We do note that blinding was not feasible, as preprocedural medications and their implications for complications must be reviewed by the operator. A study addressing this same question prospectively would nevertheless have greater validity.

In summary, this retrospective review of endosonographic needle aspiration performed on patients for whom clopidogrel must be continued demonstrates a reasonable risk profile. In the majority of cases in this study, a new diagnosis of malignancy was made. If the implications of a diagnosis made by endosonographic needle aspiration would have an important impact upon clinical decision making, it is reasonable to proceed.

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