Effect of Clopidogrel With and Without Aspirin on Bleeding Following Transbronchial Lung Biopsy*

Momen M. Wahidi, MD; Robert Garland, RRT; David Feller-Kopman, MD; Felix Herth, MD, FCCP; Heinrich D. Becker, MD, FCCP; and Armin Ernst, MD, FCCP

Background: Clopidogrel, a potent inhibitor of platelet aggregation, is being commonly prescribed in the elderly population due to its benefits in patients with atherosclerotic diseases. It is currently unknown whether clopidogrel increases the risk of bleeding during invasive pulmonary procedures.

Methods: Pigs of the Yorkshire species were randomized to one of the following two arms: clopidogrel (75 mg/d) alone; or clopidogrel plus aspirin (75 mg/d and 325 mg/d, respectively). The animals underwent flexible bronchoscopy with transbronchial lung biopsies under fluoroscopic guidance at baseline and after 1 week of daily oral intake of their assigned drugs. The main outcome of the study was the quantity of blood collected through the bronchoscope following transbronchial lung biopsy (TBLB).

Results: Sixteen animals were enrolled in the study, with 8 animals randomized to each arm. No statistically significant difference was found in the average quantity of blood resulting from transbronchial lung biopsies between procedures performed at baseline and those performed after animals received either clopidogrel (mean ± SD dose, 1.41 ± 1.14 mL) or clopidogrel plus aspirin (mean dose, 1.75 ± 1.28 mL; p = 0.42).

Conclusions: Clopidogrel, with or without aspirin, does not increase bleeding complications after TBLB in healthy pigs.

Key words: bronchoscopy; biopsy; clopidogrel; hemorrhage; swine

Abbreviations: FB = flexible bronchoscopy; TBLB = transbronchial lung biopsy

Clopidogrel (Bristol-Myers Squibb; New York, NY) is a thienopyridine compound that inhibits adenosine diphosphate-induced platelet aggregation.1 It has been shown to have beneficial effects in the prevention of thrombosis in patients with acute coronary syndrome, coronary artery stenting, and cerebrovascular disease.2–8

In a large randomized clinical trial2 in 12,562 patients presenting with acute coronary syndrome without ST-segment elevation, the rate of major bleeding complications (ie, GI bleeding and bleeding at the sites of arterial punctures) associated with clopidogrel therapy was found to be higher than that with aspirin therapy alone (relative risk, 1.38). However, there was no difference between clopidogrel and aspirin in the incidence of life-threatening or fatal bleeding. Several reports9–12 have indicated an increased risk of bleeding when clopidogrel therapy was combined with other antiplatelet drugs.

There are currently no data addressing the effect of clopidogrel on the risk of bleeding during invasive pulmonary procedures such as transbronchial lung
biopsy (TBLB) via flexible bronchoscopy (FB). The consequences of massive bleeding in the small volume of the tracheobronchial tree can be catastrophic.

Pulmonologists are increasingly encountering patients who require FB with TBLB while receiving therapy with antiplatelet drugs. This is in part due to the common risk factors of atherosclerotic disease and lung cancer, as well as an aging and growing population in the industrialized world.

In a recent survey on TBLB, clopidogrel therapy was withheld by 61.3% of pulmonologists prior to a planned TBLB for an average period of 5 days. This practice is not supported by scientific data and may cause potential harm by withholding medications with proven benefits. The aim of this study was to investigate the effect of clopidogrel, with and without aspirin, on the bleeding complication associated with TBLB in pigs.

**Materials and Methods**

**Study Design**

This investigation was designed as a randomized blinded study. The main outcome was the quantity of blood collected bronchoscopically following TBLB.

**Animals**

The Institutional Animal Care and Use Committee at the Beth Israel Deaconess Medical Center approved the experiment protocol. Pigs were chosen for this study primarily based on the resemblance of their coagulation system to that of humans. Another important factor in the choice was the similarity of the lung anatomy of pigs to that of humans. With the exception of the right upper lobe bronchus arising from the trachea, the airways pigs have similar tracheobronchial trees, as well as mucosal and tissue characteristics. Pig models have been used previously in bronchoscopy training, research on airway stenosis, malacia, airway stents, and, most relevant to our study, TBLB experiments. We selected the Yorkshire pig species due to the proximity of the average weight of the animals to that of adult humans. This allows the use of the recommended adult human dosages of clopidogrel (75 mg/d) and aspirin (325 mg/d) in the study animals.

Animals were procured for medical purposes and were free of lung diseases. They were housed in the animal facility at Beth Israel Deaconess Medical Center and were quarantined for 48 h prior to study entry.

**Description of Procedure**

**Baseline Procedure:** After an overnight fast, the procedure was performed early in the morning to ensure adequate time for recovery and proper monitoring. The animal was initially sedated with ketamine (20 mg/kg IM). A peripheral venous access was established, and baseline laboratory tests were obtained including CBC, platelet count, prothrombin time, partial thromboplastin time, and BUN and creatinine levels. A dose of cefazolin (35 mg/kg IM) was administered to prevent infectious complications. General anesthesia was induced with the IV injection of thiopental (5 to 10 mg/kg IV) and the inhalation of isoflurane (concentration, 3 to 5%). The level of anesthesia was adjusted to achieve adequate sedation and maintenance of spontaneous breathing. An endotracheal tube was placed to secure access to the airways and to facilitate bronchoscopy.

Oxygen saturation was maintained at >90% during the procedure using supplemental oxygen. No lidocaine or saline solution was administered through the working channel of the bronchoscope throughout the procedure to avoid the inaccurate measurement of bloody return.

Five TBLB specimens were obtained from the right caudal lobe under fluoroscopic guidance. Any resultant blood was suctioned into a chamber that was connected to the working channel of the bronchoscope. Following the last biopsy, the bronchoscope was kept in the airways of the animal for 5 min to ensure the suctioning of all subsequent blood. At the end of the procedure, fluoroscopy was used to detect any pneumothorax.

Postprocedure care consisted of the administration of analgesics (buprenorphine, 0.01 mg/kg IM, and a fentanyl patch, 2 µg/kg/h), the monitoring of vital signs, and close observation of the respiratory status (ie, the development of respiratory distress, persistent cough, or hemoptysis).

**Randomization and Drug Administration:** Following the baseline bronchoscopy, animals were observed for 24 h then were randomized to one of two study arms based on the following computer-generated random order: clopidogrel (75 mg/d) or clopidogrel plus aspirin (75 mg/d and 325 mg/d, respectively) for 6 to 7 days. The duration of drug administration was decided based on the pharmacodynamics of clopidogrel, as peak activity is reached within 3 to 5 days. Drugs were fed to the animals every morning concealed in a sweet-tasting treat.

**Post-Drug Procedure:** Bronchoscopy with TBLB was repeated 24 h after the last dose of the drug was administered in an identical fashion to the one described in the baseline procedure section. Bronchoscopists were blinded to the arm to which the animal was assigned. Animals were killed 48 h following this procedure.

**Statistical Analysis**

The sample size was calculated using an α level of 0.05, a β level of 0.9, and the assumption of a significant difference in blood quantity of 50 mL from before the procedure to after the procedure. Most investigators agree that a quantity of airway blood of <50 mL would rarely lead to clinically significant effects. The quantities of blood obtained following the procedure were expressed as the mean ± SD. The differences between the pre-drug administration and post-drug administration quantities of blood were assessed with a two-sided paired Student t test. The data were considered to be statistically significant at p < 0.05. A statistical software package (SAS, version 8.0; SAS Institute, Cary, NC) was used for data analysis.

**Results**

Sixteen animals were enrolled in the study. Baseline characteristics and drug assignment data are summarized in Table 1. The mean weight on study entry was 70.49 ± 4.47 kg.

Baseline laboratory test results, including platelet counts, were all within normal limits. Five biopsy specimens were obtained from the right caudal lobe with a median of six passes.
The mean quantity of blood resulting from TBLB was 1.41 ± 1.14 mL prior to receiving any drugs and 1.75 ± 1.28 mL after receiving the assigned drugs (including both the clopidogrel-alone group and the clopidogrel-plus-aspirin group). No statistically significant difference was found between medicated and nonmedicated animals (p = 0.42).

Additionally, there was no difference in the quantity of blood resulting from TBLB between animals medicated with clopidogrel (2.06 ± 1.76 mL) and those medicated with clopidogrel plus aspirin (1.44 ± 0.42; p = 0.34). Complications of the procedure included a small pneumothorax in one animal, which was detected on fluoroscopy with no subsequent clinical sequelae or need for intervention, and accidental extubation in one animal and secondary to excessive coughing necessitating reintubation and transient hypoxia in two animals.

**Discussion**

FB is a safe procedure with a low rate of complications.26,27 Bleeding is an uncommon complication that occurs more frequently following TBLB.24 It is usually self-limited with no clinical consequences. However, when the bleeding is massive or intractable, respiratory failure, and even death, can ensue.28

Since the introduction of TBLB in the 1970s, many authors have warned of the perils of TBLB in the presence of high-risk conditions such as coagulopathy, chronic renal insufficiency, liver failure, and immunosuppression.29 There are no specific data regarding the risk of bleeding following TBLB when patients are receiving anticoagulant or antiplatelet medications.

Comprehensive bronchoscopy guidelines,30 published in 2001 by the British Thoracic Society, recommend the temporary discontinuation of therapy with oral anticoagulants prior to TBLB. Antiplatelet drugs were not included in these recommendations. As bronchoscopists are faced with newer and more potent drugs that have inhibitory effects on the platelets, the decisions to withhold or continue therapy with these drugs are made based on personal experiences. The once widely held belief that aspirin should be discontinued before TBLB has been challenged by the results of a large comparative clinical trial.31 The study found no difference in TBLB-related bleeding between a control group and a group of patients taking aspirin. Whether this finding can be extrapolated to the more potent inhibitor of platelet aggregation clopidogrel remains to be proven.

Clopidogrel has been reported9–11,32–34 to cause bleeding complications following procedures in the lung and other organs such as percutaneous radiofrequency ablation of lung cancer, coronary artery bypass surgery, neurointerventional procedures, extracorporeal shock lithotripsy, and colonoscopic polypectomy. The data in these studies came either from case reports or larger series in which the results were confounded by the use of combinations of antiplatelet agents.

In our study, the animals had comparable quantities of blood following TBLB at baseline and after they had received 1 week of therapy with clopidogrel or clopidogrel plus aspirin. Furthermore, the combination of aspirin and clopidogrel did not lead to more severe bleeding compared to that with clopidogrel alone.

### Table 1—Baseline Characteristics and Drug Assignment of Animals*

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Sex</th>
<th>Weight Upon Study Entry, kg</th>
<th>Drug Assignment</th>
<th>Duration of Drug Administration, d</th>
<th>Quantity of Blood Following TBLB at Baseline, mL</th>
<th>Quantity of Blood Following TBLB After Drug Administration, mL</th>
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<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>73</td>
<td>Clopidogrel</td>
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<td>2</td>
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<tr>
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<td>79</td>
<td>Clopidogrel + ASA</td>
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<td>2</td>
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<tr>
<td>4</td>
<td>Female</td>
<td>66</td>
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<tr>
<td>5</td>
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<td>69.4</td>
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<td>0.5</td>
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<tr>
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<tr>
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<tr>
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<td>Clopidogrel</td>
<td>7</td>
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</table>

*ASA = acetylsalicylic acid.
Bronchoscopy was performed in healthy pigs, and the results of this study may not hold true in animals with atherosclerotic disease or malignant and inflammatory conditions in which abnormal lung parenchyma is present. However, our findings are compelling enough to justify a human study in which patients, who are already taking clopidogrel and have an indication for TBLB, are randomized to continue therapy with their medication or withhold it prior to the procedure.

In summary, our study demonstrated the safety of TBLB in animals that had been treated with the potent platelet inhibitory drug clopidogrel, with or without aspirin. Human investigations are needed to verify these findings in patients undergoing TBLB, especially those with underlying atherosclerotic disease or high-risk comorbidities.

References