Author's response to reviews

Title: A Novel Approach to Control Air Leaks in Complex Lung Surgery: A Retrospective Review

Authors:

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Version: 2 Date: 6 May 2012

Author's response to reviews:

Dear reviewers,

Thank you for the opportunity to respond to the thoughtful and constructive comments regarding the manuscript, A Novel Approach to Control Air Leaks in Complex Lung Surgery: A Retrospective Review.

I will respond to each of the reviewer’s comments separately.

Reviewer: K. Adam Lee
Compulsory Revisions:

1. Progel FDA approved for thoracotomy approach, off label at this current time for the VATS approach.

-The following revision has been made to the Introduction section (pg 4): “We report here our experience with the FDA-approved pleural air leak sealant Progel® (Neomend, Inc. Irvine, CA), for the treatment of air leaks incurred during open thoracotomy after standard visceral pleural closure.” This acknowledges the current FDA approval based upon the Progel Instructions for Use. The Instructions for Use has been added to the references.

-In addition, the following clarification was added to the Results section (pg 7): “It is noted that Progel is intended for application to visceral pleura during an open thoracotomy after standard visceral pleural closure with, for example, sutures or staples, of visible air leaks (# 2 mm) incurred during open resection of lung parenchyma [12].”

2. Use of Progel during decortications, was sealant used in patients with empyemas and active infection?

-Progel was used in patients with empyemas and those with active infection. The following statement was added to the Results section (pg 7): “In the decortication procedures, the majority were due to empyema, including in both the PSG and CG those with active infection, and few cases of malignant effusion with tumor peel.”
3. Would like to see the endpoint data more specific to the resection types for comparisons: ie wedge vs wedge, lobectomy vs lobectomy.

-While this is an important clinical question, the current study protocol did not call for an analysis of surgery type subgroups and the study was not powered, based upon the size of the patient population, for a statistically meaningful comparison. Larger studies may be able to provide such an analysis.

-No revisions were made in the manuscript regarding this point.

4. Discuss cost of sealant vs control population, and is one or two vials utilized.

-The following revisions to the manuscript have been made.

-In the Methods section (pg 6) the following was added in clarification: “In all cases a single one vial (4 mL) Progel kit was used.”

-In the Discussion section (pg 14) the following statement was added: “While this study did not address directly the issue of cost of care, an implication of the reduction in the length of stay observed in the pleural sealant group is that healthcare costs would be reduced in association with sealant use. Handy et al have recently reported that reductions in the length of stay following lobectomy or pneumonectomy result in substantial cost-of-care savings [17].”

-As a result of this revision, a new reference (Handy et al Ann Thorac Surg 2011) was added.

Reviewer: David Cziperle

Discretionary Revisions:

1. Minor clarification will eliminate any confusion that one may infer that the control group "standard surgical technique" may have included other forms of lung sealants.

-The pleural sealant used was Progel. This was the only sealant used. The control group was not treated with any sealant.

-To clarify this point, the following statement was added to the Results section (pg 8): “No sealant application of any type was used in in the control group.”

Reviewer: John Snider

Minor Essential Revisions:

1. The first sentence on page three refers to institutional experience that ProGel is completely reabsorbed from the lung surface one month after surgery. How is the author aware of this fact at his institution were there re-explorations?

-Per study protocol, there were no re-explorations.

-Data regarding the time of complete sealant (Progel) reabsorption is based upon the preclinical study of the sealant conducted by Kobayashi. The following statement has been added in clarification to the Introduction section (pg 4):
“Based upon the clinical experience at our institution and preclinical study, Progel is biodegradable and is completely reabsorbed from the lung surface within 14 days following surgery [11].”

2. Page 8, duration of chest tube drainage is reported as mean and median values,

the associated p value mentioned is ambiguous. According to Figure 2 both measures (mean and median) were significantly different, however the p values for the means and medians were not the same.

- The wording of the Results section (pg 9) has been revised to clarify the p values for the mean and the median chest tube duration: “The difference between the pleural sealant group and control group in both mean and median chest tube duration values was significantly different (Figure 2). The mean chest tube duration was 1.19 ± 0.52 days in the pleural sealant group compared with 3.21 ± 2.14 days in the control group, (p<0.00001). The median chest tube duration was 1.0 day (range, 1 to 3) in the pleural sealant group compared with 2.5 days (range, 1 to 7) in the control group (p<0.0001).

3. While [the single center, single surgeon design] is useful in this report, widespread acceptance will usually be reserved for a prospective, multicenter trial demonstrating not only a statistical validity but equally important a clinical advantage.

- Prospective, multicenter, studies offer advantages not found in single center, single surgeon studies. The manuscript acknowledges this in the statement in the Conclusions section (pg 15): “Further prospective randomized studies with focus on chest tube duration and hospital length of stay may add further value and confirm our results.”

4. The author compares the current results to previous studies, notably to a previously published study by Allen et al, reference 2. He acknowledges a smaller percentage of anatomic resections (lobectomy/segmentectomy :28% in the manuscript vs. 58% in the Allen paper). These cohorts appear dissimilar. To address this concern the author cites a report in Chest in 2000 by Stephan et al in which prolonged air leaks are not correlated to type or magnitude or pulmonary resection. Does this current manuscript purport to address prolonged air leaks? If so what is the definition of a prolonged air leak?

- The definition of a prolonged air leak is clarified in the Introduction (pg 4) with the statement: “…with persistence beyond 7 days in 15%-18% in patients experiencing complications resulting in prolonged air leaks [2-7].”

- The Discussion section (pg 12-13) has been revised to clarify the value of the findings of this study with the Allen trial with respect to prolonged air leaks: “There was a notable difference between the two study populations with respect to the predominant type of lung resection (54% single wedge resection in our study versus 58% lobectomy in the Allen et al trial). However, this difference is not considered to prevent a comparison between the two trials because, in a retrospective review of risk factors associated with postoperative pulmonary
complications in 266 lung resection patients, where prolonged air leak, defined as >7 days, was one of the predominant complications, the type of lung resection was not found to be a significant risk factor [16].

5. It appears that this report with its very impressive results (both statistical but even more so clinical) seems to address short term or very short term air leaks not prolonged in the usual sense.

- The air leaks in this study were detected immediately intra-operatively or within the first week of recovery.

- The purpose of the study was to determine the efficacy of Progel used intra-operatively to reduce the duration of air leaks. Using chest tube duration as an indicator of the duration of air leaks, the sealant group had no prolonged air leaks although prolonged air leak was apparent in the control group.

6. Finally noting these excellent clinical results, perhaps the author could describe more completely the surgical technique, particularly those utilized when an air leak is evident. Also were there any post operative management strategies which also enhanced the outcomes?

- To clarify the surgical techniques used, the following statement was revised in the Results section (pg 8): “There were no differences in the postoperative management of patients in either group.”

- The sealant application methods used are described in the Methods section (pg 6).

Thank you for the careful review of the manuscript and the opportunity to clarify the above points.

Sincerely,

Ara Klijian, MD