Author's response to reviews

Title: Microporous Polysaccharide Hemosphere Absorbable Hemostat Use in Cardiothoracic Surgical Procedures

Authors:

Brian A Bruckner (BABruckner@houstonmethodist.org)
Lance N Blau (lnblau@houstonmethodist.org)
Limael Rodriguez (lerodriguez26@yahoo.com)
Erik E Suarez (eesuarez@houstonmethodist.org)
Uy Q Ngo (uqngo@houstonmethodist.org)
Michael J Reardon (MReardon@houstonmethodist.org)
Matthias Loebe (MLoebe@houstonmethodist.org)

Version: 2
Date: 5 July 2014

Author's response to reviews: see over
Author’s response to reviews

Title: Microporous Polysaccharide Hemosphere Absorbable Hemostat Use in Cardiothoracic Surgical Procedures

Authors:

Lance N. Blau, MD: lnblau@houstonmethodist.org
Limael Rodriguez, MD: lerodriguez26@yahoo.com
Erik E. Suarez, MD: eesuarez@houstonmethodist.org
Uy Q. Ngo, PA-C: uqngo@houstonmethodist.org
Michael J. Reardon, MD: mreardon@houstonmethodist.org
Matthias Loebe, MD, PhD: mloebh@houstonmethodist.org

Version: 2 Date: 1 July 2014

Author’s response to reviews: see over
Reviewer's report

Title: Microporous Polysaccharide Hemosphere Absorbable Hemostat Use in Cardiothoracic Surgical Procedures

Version: 1
Date: 5 May 2014
Reviewer: Heyman Luckraz

Reviewer's report:

The Authors
Re: Microporous hemosphere absorbable haemostat use in cardiothoracic surgical procedures

It is a well-written manuscript with the largest series regarding these “haemostats” (Arista). However, as presented in the manuscript, the data needs re-organising and the authors should try as much as possible to compare “apples with apples” (please see my comments below)

The authors should provide some clarification regarding the following:

1. This is a comparison involving the “control” group being a historic group (2009-2011). How can the authors ensure that the differences that they describe between the two groups are not due to (i) the surgeon improving his skills over that period, (ii) the team working better as a team and (iii) changes in practice such a transfusion triggers and other devices.

We have included a more detailed description of our surgical practice in the revised paper. The surgical practice consisted of 2 cardiothoracic surgeons with at least 5+ yrs of experience starting in 2009. The same surgeons did all the cardiothoracic procedures requiring cardiopulmonary bypass from 2009 until 2013. We also state there were no major changes in surgical protocol/technique or transfusion triggers at our institution.

2. There were 103 patients who were treated with “Arista” and 137 patients in the other group treated with a variety of other agents. The authors should try and match these two groups as a 1:1. Moreover, they should use some risk scoring system such as STS Score in the matching process so that they are comparing “apples with apples”.

We have further clarified that in our procedures included in both groups in this study all required cardiopulmonary bypass support. The use of the bypass machine with heparinization was the common theme in our procedures. Agree, more meaningful conclusions could be obtained by better matching the study groups and risk stratifying (ie VADs, transplants, redo chest, circ arrest) which is what we plan to do in a future trial with larger numbers of patients and more STS data. We further add this important point to our study limitations in the Discussion section.
3. The lung transplants were performed through a clam-shell. Were these double lung transplants? Is it the author’s practice to perform lung transplants using cardiopulmonary bypass?

*The lung transplants in the study were all double lung transplants that required a clamshell incision with mediastinal exposure and cardiopulmonary bypass (added to manuscript). We did not include the lung transplants performed in our practice in which the pump was not used. The majority of our lung transplants are performed without the need of bypass and were not included.*

4. The authors report on 48-hour chest drainage. Do the authors believe that the drainage was still “Blood loss”? Or could this represent serous drainage? What was the haemoglobin level of the drain fluid at that point in time? It would have been better to report the first 8 hours of drainage as this would be most representative of actual bleeding.

*Due to the retrospective nature of the study and availability of data, only 24 hour chest tube outputs were available on the majority of the patients. Agree that serous drainage may represent a significant component of the chest tube output, especially in patients with heart failure. We have added this statement and limitation to our discussion section. Hgb level in drain fluid will be an important study endpoint in our upcoming prospective trial.*

5. The authors performed Scanning Electron Microscopy - this is not needed for this manuscript and should be removed. Likewise for Figure 3.

*We have added additional text to the revised manuscript which better describes these SEMs and makes their addition to our work more pertinent.*
6. The authors report on “blood units” transfused intra-op and then chose to report “mls of blood” transfused post-op. It would be better if they report on “units” rather than “mls”. Moreover, it would also be useful to report on percentage of patients receiving 1-2 units of blood and likewise for 3 or more units as it could be that only a few patients were transfused a significant amount of blood units. Moreover, the authors should elaborate on the fact that despite a significant difference in blood transfusion volume, there was no significant difference in renal failure, sepsis and ventilator dependence - all of which are known to be related to higher blood transfusions.

The data have been corrected in the post-operative period to reflect units. We also broke down the data into 1-2 units vs 3 or more in both groups and has been added to Table 3. The 1-2 unit requirement was higher in the control group (41% vs 34%) and approximately a third of the patients in each group had requirements of 3 or more units. We also added in discussion that there was no significant difference in morbidity or mortality despite the decrease in blood transfusions in the first 48 hours following surgery.

7. The authors mention that re-exploration was <5% but do not describe the actual data for each group. This needs to be included.

The unplanned re-exploration rate (<24 hrs after surgery) in both groups has been added to Table 4

8. Some of the data (e.g. ICU stay) are non-Gaussian distributed and should be reported as median rather than mean.

ICU stay (days) has been corrected to include median days with a range.

9. Can the authors define “ventilator dependence”. Did this relate to the lung transplant group?

We have added more information in Methods and data collection about our definition of morbidity as it relates to ventilator dependence, sepsis, shock, renal failure, and stroke. We defined ventilator dependence as need for vent greater than 7 days and includes entire study population.

10. Data in the manuscript are repeated in the Tables. The authors should either one or the other.

The raw data has been removed from the results section and is displayed in the Tables.

**Level of interest:** An article of importance in its field
Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests
Reviewer's report

Title: Microporous Polysaccharide Hemosphere Absorbable Hemostat Use in Cardiothoracic Surgical Procedures

Version: 1  Date: 9 May 2014

Reviewer: Zain I. Khalpey

Reviewer's report:

Research question: Does Arista influence pre, peri, and post surgical procedures?

Title: Microporous Polysaccharide Hemosphere Absorbable Hemostat Use in Cardiothoracic Surgical Procedures

Short title: Absorable Hemostat for Surgery

Abstract:

The goal of the agent under investigation is to stop active bleeding and the bleeding area while prompting clot formation. Additionally, if it had implications for application within other surgical specialties, that would be of great benefit.

The high n numbers and several endpoints are favorable. The authors have ten stated endpoints. These endpoints are relevant and feasible but do not include readmission rates.

We have added to discussion the relative short term follow-up (<30 days) of the study population and readmission rates would be important to follow-up especially in our upcoming prospective trial.

Methods: The research consists of a retrospective review of patients. The replication is feasible.

The authors state various challenges with surgical bleeding, but do not pose solutions to address each challenge mentioned early in the manuscript, therefore their study design does not seem entirely comprehensive.

We have added additional clarification and information regarding our surgical practice (ie only 2 surgeons doing all procedures during the study period, all procedures used CPB, more information on technique in surgical field) and point out additional limitations in this retrospective study including mixed population (ie VADs, transplants, and cardiac cases).
The surgical technique, though representative of the retrospective review, appears to be lacking a standardized protocol or set criteria.

*As above, we added more information about our use of topical agents, also added that surgical technique/triggers for transfusion and consistent use of topical hemostats have not changed during the entire study period, with the exception of using Arista as a topical hemostat starting in 2011.*

The SEM protocol was only completed on two experimental Arista AH patients. *We have added more description of the SEMs as it relates to the microscopic observations of Arista microspheres interacting with the surrounding blood components. We also added that more microscopic analysis will be needed in future trials/investigations in order to further elucidate the exact mechanism of hemostasis.*

Data: While the study presents its data with the inclusion of an algorithm, experimental design image, and SEM images, it is still lacking. Since non-retrospective technique such as SEM was completed, why were other quantitative analysis methods not done? For example, there is no investigation of clotting factors.

*Preoperative anti-coagulants and clotting factors will be important to look at in future trials and we have added this statement to the limitations of this retrospective study.*

Also it is not clear if a statistician was utilized for data analysis.

*Departmental statistician was used for data analysis and added to the statistics section*

Figure two contains images that are of poor quality.

*We will provide better quality images*

The SEM images are of good quality and address their research question. Other
types of microscopy or clinical imaging would enhance the article.

Agree, we are currently working with our imaging/SEM department to determine which imaging modalities would provide additional investigative clarity, that may be applied to future studies/paper submissions.

Their data yields significant findings which have direct relevance and application to the clinical setting.

Relevant standards: N/A

Discussion and conclusions: The discussion and conclusions cover all relevant information, including the acknowledgement of limitations and the application to the CT field. Future directives are not disclosed.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests