Author's response to reviews

Title: Efficacy and Safety of Active Negative Pressure Peritoneal Therapy for Reducing the Systemic Inflammatory Response After Damage Control Laparotomy (The Intra-peritoneal Vacuum Trial): Study Protocol for a Randomized Controlled Trial

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Professors or Drs. Douglas Altman, Curt Furberg, Jeremy Grimshaw, and Peter Rothwell
Editors-in-Chief, Trials
March 31st, 2013

RE: Efficacy and Safety of Active Negative Pressure Peritoneal Therapy for Reducing the Systemic Inflammatory Response After Damage Control Laparotomy (the Intra-peritoneal Vacuum Trial): Study Protocol for a Randomized Controlled Trial

Dear Editors-in-Chief of Trials:

Thank you for your thoughtful review of our manuscript and the opportunity to resubmit a revised version for consideration of publication in Trials. We feel that the appended revised manuscript is an improved report, which satisfactorily addresses each of the Reviewer’s comments. Please find below an itemized list of detailed responses to each of the Editorial and Reviewer comments, including a description of the changes made to the manuscript (which are highlighted in yellow within the manuscript text and/or tables). Within this itemized list, we first cited each comment verbatim before providing our response for ease of review.

Comments from the Editors

1. “Please also ensure that your revised manuscript conforms to the journal style (http://www.trialsjournal.com/info/instructions/). It is important that your files are correctly formatted.”

Thank you for this reminder. We have carefully reviewed the instructions for authors listed on the Trials website in order to ensure that our manuscript and its associated files conform to the journal’s requirements.

Comments from Reviewer #1

Major Essential Revisions

1. “Introduction:

Please refer to clinical studies in which IL-6 has proven to be an accurate predictor of outcome? Now, I believe only animal studies are mentioned.”

The Reviewer appropriately highlights our omission of a mention of studies in the introduction in which IL-6 was associated with poor outcomes among critically ill or injured patients. This statement had previously only appeared under the description of the primary endpoint. We therefore added the following statement to the introduction along with appropriate references (Table 1, which provides an overview of inflammatory mediators relevant to intra-abdominal sepsis or injury, has also been updated to match the statements and references included in the introduction and methods):
“These animal data are interesting as several studies have reported that the pro-inflammatory cytokine IL-6 is associated with an increased risk of organ dysfunction, adverse complications, and/or mortality among trauma victims and patients with sepsis [44-50].” (Page 8)

2. “Methods, overview:

Please indicate whether this is a superiority trial.”

We thank the Reviewer for requesting this clarification. Although we hypothesize superiority of the ABThera™ over the Barker’s vacuum pack for improving the systemic inflammatory response after damage control laparotomy, we may be underpowered to examine for evidence of superiority as this is a pilot trial. This fact has been clarified at the beginning of the methods by adding the following statement:

“Although the trial in itself may not be sufficient to establish superiority of the ABThera™ over the Barker’s vacuum pack, we hypothesize superiority, and will examine for evidence of this in hypothesis tests.” (Page 10)

3. “Intervention and comparator choice rationale:

Is there any evidence that ABThera promotes “active, equally distributed vacuum pressures”. If so, please refer to this evidence.”

We thank the Reviewer for asking whether this statement is appropriately supported by evidence. This statement derives from a description of several benchtop experiments that measured negative pressure distributions across the ABThera™ and Barker’s vacuum pack in the ABThera™ product details supplied by the manufacturer, Kinetic Concepts Incorporated. These experiments have also been described in a narrative review article [1]. However, as we could not find any published evidence to support this statement in the peer-reviewed literature, we wrote the manufacturer and kindly requested the data on file. The manufacturer confirmed that the results of this in-house experiment were presented at the Clinical Symposium on Advances in Skin and Wound Care (Oct 22-25, 2009) in San Antonio, Texas, USA as a poster conference publication. However, as they could not provide us with the study details, we have softened our statements regarding the distribution of pressures across the ABThera™ device. We also have now provided a reference to the conference poster presentation of the abstract data. Similar changes in wording have been made in the abstract and introduction sections of the manuscript. The text of the methods now state:

“The ABThera™ was chosen as the intervention as its design may allow for active, and potentially equally distributed vacuum pressures throughout the peritoneal cavity and across the viscera [58], theoretically enabling effective removal of pro-inflammatory-mediator-rich intra-peritoneal fluid. The Barker’s
vacuum pack was chosen as the comparator as it is a commonly used TAC technique, which has been recommended by the Eastern Association for the Surgery of Trauma as the current standard by which to measure other devices [59].” (Page 10)

4. “Study endpoints:
Primary endpoint:

I would suggest to blind the investigator performing the laboratory tests for treatment strategy/randomization.”

We thank the Reviewer for this suggestion. We agree, and apologize for the omission of the description of this procedural detail from our manuscript. The investigator performing all of the laboratory analyses has been blinded to treatment allocation status since the trial began, and will remain blinded until these analyses are completed. The manuscript therefore now states:

“The levels of the mediators listed in Table 2 will be determined using Luminex® technology (EMD Millipore) by an investigator blinded to TAC dressing allocation status.” (Page 18)

5. “Sample size:

Please include data on the feasibility of the sample size. How many patients are potentially eligible in your hospital for example each year?

Please mention whether this is a superiority trial.

Thank you for these requests. We have added a description of data on the feasibility of the sample size. Based on these data, we expect to complete the study in two years from its initiation. The manuscript now contains the following description:

“As there are approximately 40 to 50 patients who undergo damage control laparotomy and open abdominal management per year at our institution, this trial should able to be completed within a two year time period.” (Page 20)

With regards to whether our study is a superiority trial, please kindly refer to our response to Reviewer question 2 outlined above.

6. “Statistical Analyses, last paragraph:

I do not fully agree with the explanation to not to correct for multiple statistical tests. When using an assay with many cytokine outcomes the chance of finding a significant difference caused by multiple testing is substantial. In my opinion a correct is necessary. Although the findings will be explanatory, significant findings in favor of ABThera will be presented as such. Please comment.”
The Reviewer appropriately highlights the complexity of preventing false positive statistical discoveries when the number of statistical hypothesis testing procedures will be large. We had originally decided not to correct our p-values as statistical techniques that attempt to control the familywise type I error rate (the probability of making at least one false positive rejection among all hypotheses tested) are overly conservative and may substantially reduce the power to detect a difference [2, 3]. These methods, which include the Bonferroni approach and several others, are especially not ideal when the number of tests is large because the level of significance required to reject the null hypothesis becomes too stringent [2, 3]. A highly stringent alpha- or significance-level in a pilot study may prevent detection of a signal between the groups, as only very extreme differences between groups would be judged to be significant under the null hypothesis [3].

However, as we agree with the Reviewer that significant findings in this study may be viewed in favor of the ABThera™, we have opted to control the false positive detection rate using the validated approach developed by Benjamini and Hochberg [4-6]. This approach is commonly used and frequently recommended in studies where a large number of statistical comparisons will be made, including DNA microarray and other similar types of studies [3]. This procedure uses a false discovery rate, rather than an overall probability of rejecting the null as the criterion for judging whether a pairwise difference is statistically significant [4]. The false discovery rate is defined as expected proportion of null hypotheses that are falsely rejected divided by the total number of rejections [4]. The testing procedure ensures that under the null hypotheses for multiple tests, we would expect that 5% of significant test differences would be false positive discoveries [4]. The false discovery rate procedure increases power at the cost of increasing the rate of type I errors, but not above a preset acceptable threshold (e.g., 5%). As an example, if we conducted 100 statistical tests, setting the false discovery rate at 5% would ensure that only 5 were type I errors.

In order to reflect our control of the false discovery rate in our analyses, we have added the following text to the manuscript:

“As the number of conducted statistical tests will be large, we will use the false discovery rate (FDR) procedure developed by Benjamini and Hochberg to restrict the proportion of incorrectly rejected null hypotheses to 0.05 [79-81]. All tests will be two-sided, and only those with an FDR-corrected p-value (i.e. q-value) <0.05 will be considered statistically significant [79].” (Page 22)

7. “Discussion:

Please also address that planned relaparotomy is not the evidence based strategy of choice for secondary peritonitis (see RELAP trial, van Ruler et al. JAMA 2007)”
We thank the Reviewer for asking us to address that planned relaparotomy is not the evidence based strategy of choice for secondary peritonitis. We agree with the Reviewer that our study should be compared to this previous study in order to enhance clarity for the readers of this trial protocol. In our trial, study patients in both treatment arms will undergo planned re-operation with attempts at abdominal fascial closure approximately 24- to 72-hours after damage control laparotomy. Although the RELAP trial reported that planned re-laparotomy after an initial emergency laparotomy for secondary peritonitis resulted in increased health care utilization and costs as compared to re-laparotomy on-demand [7, 8], these findings likely cannot be generalized to our study’s source population. In the RELAP trial, the investigators excluded patients that were managed with temporary operative techniques such as intra-abdominal gauze packing and stapled intestinal resections without reanastomosis [7]. Moreover, only 11% of the patients allocated to planned re-laparotomy received open abdominal management while the remainder underwent intraoperative primary fascial closure [7]. Thus, very few of the patients in the planned re-laparotomy group likely received damage control laparotomy. These between-trial differences in patient source population have now been highlighted in a paragraph in the discussion section of manuscript, which reads:

“In this trial, study patients in both treatment arms will undergo planned re-operation with attempts at abdominal fascial closure approximately 24- to 72-hours after damage control laparotomy. Although one RCT (the RELAP trial) reported that planned re-laparotomy after an initial emergency laparotomy for secondary peritonitis resulted in increased health care utilization and costs as compared to re-laparotomy on-demand [82, 83], these findings likely cannot be generalized to our study’s source population. In the RELAP trial, the investigators excluded patients that were managed with temporary operative techniques such as intra-abdominal gauze packing and stapled intestinal resections without reanastomosis [82]. Moreover, 89% of the patients allocated to planned re-laparotomy received intraoperative primary fascial closure [82]. Thus, very few, if any, of the patients in the planned re-laparotomy group likely received damage control laparotomy.” (Page 23)

8. “Table 2.

If this is a standard assay it is not necessary to show all outcomes of measurements. It is also sufficient to refer to the test and manufacturers.”

Thank you. In order to minimize bias with regards to which mediators are measured (and to gain a better understanding of which inflammatory pathways are activated after damage control laparotomy for intra-abdominal sepsis or injury), we decided to measure the peritoneal and plasma concentrations of 65 different mediators relevant to the inflammatory response. These mediators could only be measured using a unique combination of the following multiplex kits: Bio-Plex Pro™ Human Cytokine 21-plex Assay, Bio-Plex Pro™ Human Cytokine 27-plex Assay, and Bio-Plex Pro™ Human Acute Phase 5+4-plex Panel
Complete (Bio-Rad Laboratories). In addition, a Bio-Plex Pro™ Human Custom 8-Plex (IL-17F, -21, -22, -23, -25, -31, -33, and sCD-40L) (Bio-Rad Laboratories) will also be used to provide broadened coverage of Th17 cytokines. Table 2 was created as we felt that by mentioning only the test and its manufacturers, it may be unclear to some readers exactly which mediators we were going to measure in the study. We have now added a description of these multiplex kits to the manuscript. However, as we believe that Table 2 gives a ready overview of the mediators to be measured in this trial, we elected to retain Table 2 in the manuscript. However, if the Reviewer or Editors feel that this table is not needed, we would be happy to remove it from the final article.

9. “Figure 1.
Please adhere to the CONSORT guidelines to show the flow of participants, including lost to follow-up etc.”

We thank the Reviewer for this request. We have created a CONSORT flow diagram [9] and included this as the new Figure 1 in the manuscript. We also created an abbreviated/truncated version of the original Figure 1 (which has now been relabeled Figure 2) as this diagram outlines the timing and location of sample collections. It also shows which outcomes will be analyzed using per-protocol versus intention-to-treat procedures. These two diagrams now provide a complementary and complete overview of the study design.

10. “Additional comment:
Would it be possible to show a picture of drawing of the different closure devices? That would be insightful for readers.”

We thank the Reviewer for this suggestion. As we lacked the experience to create a detailed illustration of the different temporary abdominal closure devices, we recruited the help of a graphic designer at the University of Calgary. The manuscript now contains two high-resolution images of the ABThera™ and Barker’s vacuum pack that match our descriptions of its application completely (Figures 3 and 4, respectively). We hope that this will be insightful for readers.

Minor Essential Revisions

11. “Introduction, section paragraph:
What is mechanical hemorrhage?”

We thank the Reviewer for asking for clarification on the meaning of this term. We had attempted to use the term “mechanical” to describe hemorrhage resulting from an injury to a major named blood vessel associated with active extravasation of blood (e.g., a penetrating injury to the inferior vena cava), as opposed to diffuse, coagulopathic oozing. As this is not clear to readers, we have removed the word “mechanical” from this sentence in the introduction.
Thank you once again for the kind and thoughtful reviews of our manuscript. The comments of the Reviewer have improved our manuscript and are deeply appreciated. We hope that you will find this version suitable for publication in Trials, and look forward to your response.

Sincerely,

Derek J. Roberts, MD and Andrew W. Kirkpatrick, MD, MHSc for the authors.

References


