Author’s response to reviews

Title: PRESERVATION OF RENAL FUNCTION IN CARDIAC SURGERY PATIENTS WITH LOW CARDIAC OUTPUT SYNDROME: LEVOSIMENDAN VS BETA AGONISTS

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Author’s response to reviews:

Dear editor,

We would like to thank you and the reviewers for your thorough reading of the paper and for your constructive comments. We have improved the paper according to your suggestions and put changes in red. We hope that the new version will respond to all your comments.

Please, find below a point by-point response to reviewers’ comments.
Reviewer reports:

(Reviewer 1): Thank you for doing a valuable work and fascinating subject. I read this manuscript and with following questions and comments I hope can help you to write the manuscript more scientifically.

- Regarding the title of manuscript it sounds to me that your all subjects had had renal failure before allocating to the study, so I suggest you it is better to delete "AND RENAL FAILURE". Thank you. Following your suggestion, we deleted this part.

- In background section you mentioned that levosimendan improves cardiac contractility without increasing myocardial oxygen consumption. Of course it increases oxygen consumption but it is less compared to other inotropes. (Journal of Cardiovascular Pharmacology Apr 2004, 43(4):555-61 *).

Thank your for your valuable observation. We changed this statement.

- In method section:

* line 5 it seems that it is cardiac index not cardiac rate.

We changed it.

*It is still not clear when and how you allocated two groups of your study? What was your inclusion and exclusion criteria and what is type of your study?

Thank you. We included a detailed description of our inclusion and exclusion criteria (please, see below).

Again I am not sure how did you collect your data and when?

Thank you. We inserted a more detailed description of our data collection method.

* Regarding your renal function there are many drugs that are been administered during surgery like Manitol, other diuretics, did you notice these and how you adjust them between two groups?

All patients were administered furosemide (only diuretic used in our study), without any significant differences between groups in terms of dose. We inserted the following discussion in the manuscript: “There were no significant differences between groups in the use of furosemide (only diuretic used in our study) (p>0.05).”

- In discussion section:

- The first sentence is confusing, whether it's your opinion and from your study results or you are implying to previous other studies? How you conclude from your study that levosimendan
acts as an inodilator? And what's other different mechanisms that we can conclude from your study that preserves renal function?

We have changed it as follows: “The effect of levosimendan could be two-fold: first, its inotropic effects may improve cardiac output. Secondly, in a setting of low cardiac output, levosimendan has a direct effect on renal perfusion as it opens potassium channels in arteries, thereby causing vasodilation. In addition, in a setting of renal hypoperfusion due to decreased cardiac output, levosimendan provides kidney protection by blocking potassium channels at mitochondrial level (11-15).”

- It is not clear who and how measured cardiac index in your study? Is it done by an echo cardiologist?

Thank you. We inserted: “Heart rate was continuously monitored using MostCare® (). Ejection fraction of the left ventricle (EFLV) was monitored by an ultrasound specialist.”

(Reviewer 2): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Dear editors, this article needs major essential revisions:

Background:

At first in abstract:

1- The aim of the study is a little different with the title.

Thank you for your comment. We changed the title to “Preservation of renal function in cardiac surgery patients with low cardiac output syndrome: Levosimendan vs beta agonists.”

2- Please write the type of your study.

Following your suggestion, we included the following description: “Patients were divided into two groups based on the therapy received. Thus patients were allocated either to receive beta agonists or levosimendan at physician’s discretion.”

3- In conclusion, it is better to write the possible effect of levosimendan is protective role against renal dysfunction.
We included: “We investigated the potential protective role of levosimendan against renal dysfunction in these patients.”

4- Method:

page 5: Methods:

First paragraph, line 5, cardiac rate needs to change in cardiac index.

Changed.

First paragraph, line 5, 2 l/min/m2.

Changed.

Please discuss your methods to measure cardiac output in perioperative and postoperative phases.

We inserted a description of the methods used to measure cardiac output.

How many days you follow these patients?

We included: “the following data were collected from recruitment to ICU discharge.”

What is your goal for tapering of beta agonists and levosimendan?

We included:”The objectives of the therapy in the two groups were reaching a CI > 2 l/min/m2 and a central venous saturation > 65% following volume replacement.”

Did you have any patients who need mechanical support?

No, we didn’t. We clarified it in the manuscript.

Results:

Please insert p values in all tables.

We added it.

In table 3, ns means not significant, please write it.

We added it.
Please correct table 2, in this table the number of patients with no renal failure: 103, with renal failure :103 , but the total participants are 15.

Corrected.

Discussion:

Do not you have any limitations in this study?

We inserted the following paragraph: “The main limitation of this study was that patients were not randomized to treatment groups. The reason is that we preferred that physicians treated their patients with the medications they were more familiar with. This may have caused bias in the interpretation of results, as physicians will probably favor conventional therapy.”

How you can define acute kidney injury in these patients?

We included: “Renal failure was classified using the Acute Kidney Injury (AKI) scale according to variations in creatinine levels and diuresis.”

(Reviewer 3): Dear Editor,

The manuscript BANE-D-18-00443R1, entitled, "PRESERVATION OF RENAL FUNCTION IN CARDIAC SURGERY PATIENTS WITH LOW CARDIAC OUTPUT SYNDROME AND RENAL FAILURE: LEVOSIMENDAN VS BETA AGONISTS" is an original study to evaluate the effect of levosimendan on prevention of AKI in low cardiac output cardiac surgery patients. The special difficult field of study could be interesting for readers; however, the manuscript suffers from several obscure points in the methodology. My concerns about the manuscript are as follows;

Abstract

The aim of study in the background is not matched with the title and method of study.

We changed it.

Method:

The type of study should be reflected in the abstract method.

We included a description of the type of study.
Conclusion:

This study just compares the effect of Levosimendan vs. beta-agonists.

The conclusion is not relevant for the results of this study. It's not possible to talk about the protective effect on one of these study groups without accounting the second arm of the study.

We changed it and included: “We investigated the potential protective role of levosimendan against renal dysfunction in these patients.”

Background

There are some grammatical errors in the manuscript. It needs a grammatical revise.

We asked a professional proofreader to correct the manuscript.

Method

Please mention the type of the study at beginning of the methods section.

Inserted.

In line 9; what means "cardiac rate"?

We changed it.

Please re-check all units among the text.

We checked and corrected them.

The method section needs more details. Please discuss the methods used to measure cardiac output in pre- and post-operative phases and also the PAWP. How was your routine assessment methods and protocols for detecting LCOS?

We inserted a description.

How long patients were followed?

We inserted: “the following data were collected from recruitment to ICU discharge”.
When you start your intervention _ pre- intra- or post-operatively-?

We clarified in the manusscript that our intervention stasrted after cardiac surgery.

What was and how you choose your Beta-agonist?

We inserted in the manuscript: “The beta-agonists used for haemodynamic control were adrenaline or dobutamine, based on whether vascular resistances concomitant to low cardiac output were low or high. Noradrenaline was added when necessary.”

How you titrate and what was your target for beta-agonist therapy?

We included: “The objectives of the therapy in the two groups were reaching a CI &gt;2 l/min/m2 and a central venous saturation &gt; 65% following volume replacement.”

Did you have any patient who needs mechanical cardiac output support?

No, we didn’t. We clarified it in the manuscript.

How you categorized patients to enter one of the study groups? Was there any kind of randomization?

We included a description of the method of randomization and inclusion and exclusion criteria in the manuscript, as follows:” Patients were divided into two groups based on the therapy received. Thus patients were allocated either to receive beta agonists or levosimendan at physician’s discretion. Inclusion and exclusion criteria were:

1. Patients older than 18 years who developed postoperative low cardiac output syndrome (LCOS) following heart surgery.

2. LCOS (was defined as: a cardiac index &lt; 2l/min/m2, pulmonary arterial wedge pressure (PAWP) &gt; 18 mmHg or central venous saturation &lt; 65% after volume replacement

3. Patients who required inotropic support for the treatment of LCOS.

Exclusion criteria were:

1. Patients who required combined surgery (not only cardiac surgery)

2. Emergency surgery

Did you have any protocol to blinding participants to the study?

The team conducting the statistical analysis was blinded to the group analyzed.

What were your criteria to diagnose AKI?

The AKI scale. We clarified this in the manuscript, as follows: “Kidney failure was classified using the Acute Kidney Injury (AKI) scale according to variations in creatinine levels and diuresis.”

Please briefly mention other treatments for LCOS and AKI.

We clarified: “Apart from diuretics, renal replacement therapy is another therapeutic option for acute kidney injury. When response to inotropic support is not adequate, intra-aortic balloon pump (IABP) counterpulsation and other ventricular assist devices can be used. None of our patients required any of these extracorporeal therapies.”

Please discuss your statistical methods.

We inserted: “The team conducting the statistical analysis was blinded to the group analyzed. A descriptive statistical analysis will be first conducted. Continental variables will be expressed in a table as means, standard deviations or medians based on normality of distribution. If continuous quantitative variables are normally distributed –as assessed by Shapiro-Wilk test–, Student’s t-test will be performed to compare the means of two independent groups (having kidney dysfunction YES/NO). If variables are abnormally distributed, Mann-Whitney U test will be performed.

Please consider the possible confounders in the upper mention inquiries to include in a limitation section at the end of discussion section.

Following your suggestion, we included a discussion of the limitation of the study, as follows: “The main limitation of this study was that patients were not randomized to treatment groups. The reason is that we preferred that physicians treated their patients with the medications they were more familiar with. This may have caused bias in the interpretation of results, as physicians will probably favor the conventional therapy. A triple-blinded study was not possible due to the type of study. However, the team conducting statistical analysis was blinded to the group analyzed.”

Results

Please, insert all the p-values for tables 1,2 and 3.

We incorporated them.
What means the "ns" in table 3.

Explained in the text (non-significant)

Please discuss abbreviations in the footnote of tables.

Done.

In table 1 in first rows please correct the number of participants in the "No Renal Failure at Discharge (n=103)", as total participants in the group are just 15.

Corrected.

Please don't repeat data from the tables in the text.

What means * sign in table 2?

The * sign was deleted and p values were written.

Please discuss probable mortality or other major morbidities. Do you have any data to compare the Length of ICU stay or the total hospital length of stay? We clarified that no deaths occurred in any of the two groups and no statistically significant differences were observed in ICU length of stay.

Please consider a regression test to prove the results and rule-out the effect of possible confounders. A more detailed description of statistical analysis was included.

Discussion

Please consider a limitation section to include all limitations for the study. Low power of the study, possible confounders, lack of randomization, and other concerns about the study should be listed there. Added.

As an important point about the conclusion, "you should clear the definition of AKI whenever you stating the effect of levosimendan on AKI." As explained previously, our definition of AKI is based on the Acute Kidney Injury scale score.

AKI have a wide range of definition. Furthermore, the low power of the study limits the popularity of the conclusion. It's better to limit the conclusion for the results of this study. We changed it, as follows: “The incidence of kidney failure decreased with the postoperative
administration of levosimendan to cardiac surgery patients with LCOS as compared to beta-agonists. “

Thank you.