Author's response to reviews

Title: Effects of thoracic epidural analgesia on plasma cAMP and cGMP levels in patients with heart failure

Authors:

Qingshu Li (liqingshu1985@163.com)
Fengqi Liu (liqingshu1985@126.com)

Version: 4 Date: 30 August 2013

Author's response to reviews: see over
Introduction -

Introduction needs to be expanded with more emphasis on the relevance of epidural anaesthesia to heart failure with support of literature. At present there is only one selfcitation.

Heart failure is the final stage for several types of heart diseases and many related illnesses. Although the use of cardiotonic drugs, diuretics, β-blockers, and angiotensin-converting-enzyme inhibitors (ACEI) can improve the cardiac function in patients with heart failure [1-3], the morbidity and mortality of heart failure continues to remain high [4, 5]. Therefore, it is indispensable to search for new treatments for heart failure. In the past two decades extensive investigations have developed several effective approaches for reducing the morbidity and mortality of patients with congestive heart failure. These include pharmacological [2, 3, 6] and cardiac device therapies [7], but significant improvement on the clinical outcome has not been observed. Recently, cell-based therapy has been demonstrated as an effective method for treating heart failure in vitro and in vivo [8].

Sympathetic hyperactivity is a compensatory response to cardiac function that can activate several signal transduction pathways [9], but eventually becomes part of the disease process and may result in worsening cardiac function. It was speculated that inhibiting the hyperactive sympathetic nervous system would correct the abnormal signal transduction and improve the cardiac function in patients with heart failure. High thoracic epidural analgesia (TEA) been used extensively to treat myocardial infarction patients with severe chest pain, with a major mechanism of action being selective blockading of cardiac sympathetic [10, 11]. Kock et al. have reported that TEA can improve the left ventricular function during stress-induced myocardial ischemia in patients with coronary artery disease [12]. In addition, we have previously reported a satisfying outcome by one patient treated with TEA [1]. Based on these preliminary results, this clinical study was designed to demonstrate the therapeutic efficacy and safety of the TEA treatment in a clinical trial setting. The results will be useful for improving the clinical outcome of TEA in patients with heart failure.

Methods –

Please do not mention the type of NYHA class the patients were before starting treatment. This suggests randomization was not properly done.
Mention them in the result section.

Forty patients (including 32 males and 8 females) with heart failure were randomly divided into two groups: (1) the thoracic TEA group (including 17 males and 3 females) and (2) control group (including 15 males and 5 females). In the TEA group, there were five case of coronary artery heart disease (CHD), four cases of hypertension, and 11 cases of dilated cardiomyopathy (DCM); the corresponding cases for these diseases in the control group were four, seven, and nine, respectively. Patients were classified according to the New York Heart Association as class IV (consisting of 28 patients, 13 in the control group and 15 in the TEA group and class III (consisting of 12 patients, seven in the control group and five in the TEA group.

Why lidocaine was used only during the daytime? Provide some justification in the discussion.

We chose the intermittent injection scheme because it’s reversible sympathetic nerve function, and can avoid failing to recruit sympathetic drive when needed to support cardiac function as a result of removal of sympathetic nerve. The patients symptomatically improved all day, also in the night without routine epidural injections.

How did you confirm that epidural catheter tip was in the T1-2 level, by any contrast study or ultrasound etc? Please mention.

Adequacy and level of the block were established by confirming loss of pin prick sensation and warm/cold discrimination. Results: please refer to the tables and figures in the text. You can include a table showing the NYHA status of patients before and after treatment in both the groups.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>LVEDD (mm)</th>
<th>EF(%)</th>
<th>FS(%)</th>
<th>NYHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>64.9±5.9</td>
<td>32.45±7.21</td>
<td>25.8±5.73</td>
<td>3.65±0.48</td>
</tr>
<tr>
<td>4weeks post-treatment</td>
<td>63.2±5.2</td>
<td>33.15±5.98</td>
<td>26.6±5.52</td>
<td>3.3±0.8</td>
</tr>
<tr>
<td>TEA group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>66.5±5.4</td>
<td>30.35±6.78</td>
<td>24.2±3.54</td>
<td>3.75±0.44</td>
</tr>
<tr>
<td>4weeks post-treatment</td>
<td>58.3±5.4*</td>
<td>34.15±6.12*</td>
<td>28.15±4.67*</td>
<td>2.55±0.76*</td>
</tr>
</tbody>
</table>

Discussion: well structured.

Why lidocaine was used only during the daytime? Provide some justification in the discussion.

We chose the intermittent injection scheme because it’s reversible sympathetic nerve function, and can avoid failing to recruit sympathetic drive when needed to support cardiac function as a result of removal of sympathetic nerve. The patients symptomatically improved all day, also in the night without routine epidural injections.
What is the ideal level of epidural catheter tip for adequate sympathetic blockade of heart? Mention with some reference.

Adequacy and level of the block were established by confirming loss of pin prick sensation and warm/cold discrimination.

- Minor Essential Revisions
  - there are many grammatical errors. Kindly correct all those

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

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
- Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? – NO
- Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? – NO
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? – NO

Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? – NO

- Do you have any other financial competing interests? – NO
- Do you have any non-financial competing interests in relation to this paper? – NO
Reviewer's report
Title: Effects of thoracic epidural analgesia on plasma cAMP and cGMP levels in patients with heart failure
Version: 1 Date: 26 April 2013
Reviewer: Peter Alston

Reviewer's report:
This is an interesting study that examines the effects of using thoracic epidural analgesia (TEA) along with standard pharmacological treatment, to treat heart failure. It examines a number of symptomatic, biochemical and surrogate outcomes. However, it has a number of limitations.

Major compulsory revisions
1. There is no information describing how the patients were selected for inclusion in the study.
   Forty patients with heart failure were randomly divided into two groups: (1) the thoracic TEA group and (2) control group using a computer-generated random number.
2. Insufficient detail of the patients characteristics and drug therapy were provided and the cause of the patients heart failure.
   The patients in the control group were treated with conventional medications (e.g., digoxin, diureticum, β-blockers, and ACEI), while patients in the TEA group were persistent TEA in addition to conventional medications. Overall, medications administered in the two groups were similar, and included β-blocker and ACE inhibitor.
3. Insufficient details regarding the randomisation and blinding have been provided.
   Forty patients with heart failure were randomly divided into two groups: (1) the thoracic TEA group and (2) control group using a computer-generated random number. This study was a single blind trial.
4. Details of the ethical approval should have been provided.
   The design for this study and clinical protocols were reviewed and approved by the Ethics Committee of First Affiliated Hospital of Harbin Medical University, Harbin, China.
5. Information regarding where the patients were during the study and how they were managed should have been provided.
   The patients were in the hospital during the study.
6. An explanation why the four week period was used should have been provided.
   We observed that the heart function of the patient with heart failure had significantly improved after TEA for 4 weeks.
7. No study population size estimate was provided to justify the sample size of the study.
   I can’t understand this question, please explain in detail.
8. Multiple testing was applied inflating the risk of Type 1 statistical error.
   Correction for multiple testing should have applied or one outcome nominated
as the primary outcome of interest and the rest as secondary outcomes. 
Has been revised.
9. Details of the reliability of the biochemical tests should have been provided as well who performed the tests.
The biochemical tests were carried out by experienced laboratory assistant who were unaware of the group assignments for the patients and their laboratory test results.
10. Details of who performed the ultrasonography should have been provided and with what kind of machine. Details of how the ultrasound measurements were performed should also have been provided.
The ultrasonography were carried out by experienced ultrasound doctor. Using The GE Vivid5 color ultrasonic diagnostic instrument was used, with the probe frequency 1.7-3.6MHz. By using M type ultrasonic, we got the measurement results of ejection fraction, fractional shortening and left ventricular end diastolic diameter.
11. Details of who performed the ultrasonography should have been provided.
We used SSPS13.0 to complete the data statistics on Windows operating system.
12. Information who gave the epidural top ups should have been provided and why the drug, dosing and timing of top-ups were chose.
The epidural top ups had been provided by experienced doctors. the drug, dosing and timing of top-ups were choses according to our clinical experience and pertinent literature.
13. There is no evidence that the distribution of the data was normal. It is likely that the biological data was of non-normal distribution and if so it should have been first transformed using something the natural logarithm so that it was near-normal distribution.
Has been revised.
14. It would have been valuable to have presented the distribution as 95% confidence intervals.
Has been revised.
15. The New York Heart Association classification of symptoms were assessed but do not appear to have been statistically analysed.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>LVEDD (mm)</th>
<th>EF(%)</th>
<th>FS(%)</th>
<th>NYHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>64.9±5.9</td>
<td>32.45±7.21</td>
<td>25.8±5.73</td>
<td>3.65±0.48</td>
</tr>
<tr>
<td>4 weeks post-treatment</td>
<td>63.2±5.2</td>
<td>33.15±5.98</td>
<td>26.6±5.52</td>
<td>3.3±0.8</td>
</tr>
<tr>
<td>TEA group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>66.5±5.4</td>
<td>30.35±6.78</td>
<td>24.2±3.54</td>
<td>3.75±0.44</td>
</tr>
<tr>
<td>4 weeks post-treatment</td>
<td>58.3±5.4$^*$</td>
<td>34.15±6.12$^*$</td>
<td>28.15±4.67$^*$$^\triangle$</td>
<td>2.55±0.76$^*$$^\triangle$</td>
</tr>
</tbody>
</table>
16. No details of the analysis of variance models were presented.
I can’t understand this question, please explain in detail.
17. Complications should have been more completely reported as it is not clear what bleeding and infectious complications are i.e. did they have epidural haematomas or abscesses. If either of these complication occurred then it outweighs any symptomatic benefits associated with TEA.
TEA group had bleeding complications, and one patient had infectious complication. No patients had venous thromboembolism complication.
Minor essential revisions. No patient withdrew from the study because of complications.
1. There is excessive duplication of results and tables. All the data could have been summarised in one table.
   There is not enough space in one table to summarize all the data, so we divided into two tables.
2. There should have been more discussion regarding the limitations of the TEA.
   Has been revised.

3. Acronyms should be defined the first time that they are used. They should also not be used in titles for figures or tables.
   Has been revised.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests'
- **Major Compulsory Revisions**

**Introduction**

Introduction needs to be expanded with more emphasis on the relevance of epidural anaesthesia to heart failure with support of literature. At present there is only one self citation. Heart failure is the final stage for several types of heart diseases and many related illnesses. Although the use of cardiotonic drugs, diuretics, β-blockers, and angiotensin-converting-enzyme inhibitors (ACEI) can improve the cardiac function in patients with heart failure [1-3], the morbidity and mortality of heart failure continues to remain high [4, 5]. Therefore, it is indispensable to search for new treatments for heart failure. In the past two decades extensive investigations have developed several effective approaches for reducing the morbidity and mortality of patients with congestive heart failure. These include pharmacological [2, 3, 6] and cardiac device therapies [7], but significant improvement on the clinical outcome has not been observed. Recently, cell-based therapy has been demonstrated as an effective method for treating heart failure *in vitro* and *in vivo* [8]. Sympathetic hyperactivity is a compensatory response to cardiac function that can activate several signal transduction pathways [9], but eventually becomes part of the disease process and may result in worsening cardiac function. It was speculated that inhibiting the hyperactive sympathetic nervous system would correct the abnormal signal transduction and improve the cardiac function in patients with heart failure. High thoracic epidural analgesia (TEA) been used extensively to treat myocardial infarction patients with severe chest pain, with a major mechanism of action being selective blockading of cardiac sympathetic [10, 11]. Kock *et al.* have reported that TEA can improve the left ventricular function during stress-induced myocardial ischemia in patients with coronary artery disease [12]. In addition, we have previously reported a satisfying outcome by one patient treated with TEA [1]. Based on these preliminary results, this isclinical study was designed to demonstrate the therapeutic efficacy and safety of the TEA treatment in a clinical trial setting. The results will be useful for improving the clinical outcome of TEA in patients with heart failure.

**Methods**

Please do not mention the type of NYHA class the patients were before starting treatment. This suggests randomization was not properly done. Mention them in the result section. Why lidocaine was used only during the daytime? Provide some justification in the discussion.
Forty patients (including 32 males and 8 females) with heart failure were randomly divided into two groups: (1) the thoracic TEA group (including 17 males and 3 females) and (2) control group (including 15 males and 5 females). In the TEA group, there were five cases of coronary artery heart disease (CHD), four cases of hypertension, and 11 cases of dilated cardiomyopathy (DCM); the corresponding cases for these diseases in the control group were four, seven, and nine, respectively. Patients were classified according to the New York Heart Association as class IV (consisting of 28 patients, 13 in the control group and 15 in the TEA group) and class III (consisting of 12 patients, seven in the control group and five in the TEA group).

How did you confirm that epidural catheter tip was in the T1-2 level, by any contrast study or ultrasound etc? Please mention.

Adequacy and level of the block were established by confirming loss of pin prick sensation and warm/cold discrimination.

Results:

Please refer to the tables and figures in the text. You can include a table showing the NYHA status of patients before and after treatment in both the groups.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>LVEDD (mm)</th>
<th>EF(%)</th>
<th>FS(%)</th>
<th>NYHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>64.9±5.9</td>
<td>32.45±7.21</td>
<td>25.8±5.73</td>
<td>3.65±0.48</td>
</tr>
<tr>
<td>4 weeks post-treatment</td>
<td>63.2±5.2</td>
<td>33.15±5.98</td>
<td>26.6±5.52</td>
<td>3.3±0.8</td>
</tr>
<tr>
<td>TEA group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>66.5±5.4</td>
<td>30.35±6.78</td>
<td>24.2±3.54</td>
<td>3.75±0.44</td>
</tr>
<tr>
<td>4 weeks post-treatment</td>
<td>58.3±5.4※</td>
<td>34.15±6.12#</td>
<td>28.15±4.67#△</td>
<td>2.55±0.76※</td>
</tr>
</tbody>
</table>

Discussion: well structured.

Why lidocaine was used only during the daytime? Provide some justification in the discussion.

We chose the intermittent injection scheme because it’s reversible sympathetic nerve function, and can avoid failing to recruit sympathetic drive when needed to support cardiac function as a result of removal of sympathetic nerve. The patients symptomatically improved all day, also in the night without routine epidural injections.

What is the ideal level of epidural catheter tip for adequate sympathetic blockade of heart? Mention with some reference.

Adequacy and level of the block were established by confirming loss of pin prick sensation and warm/cold discrimination.
there are many grammatical errors. Kindly correct all those

**Given your assessment of the manuscript, what do you advise should be the next step?**

Acceptable after the major compulsory and minor essential revisions are made.

**Level of interest**

- An article of importance in its field

**Please indicate the quality of language in the manuscript:**

- Needs some language corrections before being published

**Statistical review**

------------------

- No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests**

Please complete a declaration of competing interests, considering the following questions:

- Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? – NO
- Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? – NO
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? – NO
- Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? – NO
- Do you have any other financial competing interests? – NO
- Do you have any non-financial competing interests in relation to this paper? - NO

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.