Author’s response to reviews

Title: Bisoprolol Transdermal Patch for Perioperative Care of Non-cardiac Surgery in Patients with Hypertrophic Obstructive Cardiomyopathy

Authors:

Yoichi Imori (s9012@nms.ac.jp)
Hitoshi Takano (htakano@nms.ac.jp)
Hiroshi Mase (hiroshi-m@nms.ac.jp)
Junya Matsuda (jun1984087@nms.ac.jp)
Hideto Sangen (sangen777@nms.ac.jp)
Yuki Izumi (y-izu@nms.ac.jp)
Yukichi Tokita (yukichi@nms.ac.jp)
Takeshi Yamamoto (yamamoto56@nms.ac.jp)
Wataru Shimizu (wshimizu@nms.ac.jp)

Version: 3 Date: 31 Jul 2019

Author’s response to reviews:

Responses to the Editor and Reviewers’ Comments

We are grateful for the opportunity to submit a revised version of our manuscript, titled “Bisoprolol Transdermal Patch for Perioperative Care of Non-cardiac Surgery in Patients with Hypertrophic Obstructive Cardiomyopathy,” to BMC Cardiovascular Disorders. Here, we have provided detailed point-by-point responses to the editor and reviewers’ comments. We hope that the manuscript in its present form satisfies the editor and reviewers; however, we really appreciate further comments, if warranted.

Editor Comments:

We really appreciate your very helpful and detailed comments, to which we have provided the following responses.
This is an interesting study of transdermal bisoprolol administration to patients with HCOM undergoing noncardiac surgery. The study has a retrospective design and has included only 10 patients. Additionally, to the reviewers' comments:

Comment 1: Due to the low case number it is appropriate to use only nonparametric statistical analysis and avoid the use t-test and chi-square test.

Response: We agree that the nonparametric method is better for evaluating our data. We have changed the Abstract (page 3, lines 67-70), Methods (pages 9, lines 193-198), and Results (page 9, lines 204-205; pages 10, lines 219-224; page 11, lines 235-241), as per your advice.

Comment 2: An additional limitation of the study could be that the patients were not very symptomatic, so as to be expected to benefit from the transdermal bisprolol.

Response: We might have underestimated the efficacy of transdermal bisoprolol because we included some patients who were not very symptomatic or patients who showed improvement of their severe symptom after the prior intervention.

Hence, we have addressed this limitation as follows (page 14, lines 320-323).

“Third, we might have underestimated the efficacy of the β-blocker because we included some patients who were not very symptomatic (New York Heart Association classes I and II) or patients who experienced improvement in their severe symptom after the prior intervention.”

Comment 3: Beta-blocker therapy in HOCM is expected to lower primarily the provocable gradient (exercise, Valsalva), however, it is not clear if the provocable gradient or only the resting gradient were measured. Please elaborate on that.

Response: In order to measure the pressure gradient before and after switching therapy from oral bisoprolol to the bisoprolol transdermal patch, we assessed the resting pressure gradient using Doppler echocardiography. However, when we included patients, we diagnosed HOCM in patients with HCM, which was defined as an intraventricular gradient ≥30 mmHg at rest or on provocation. We have changed the Methods (page 8, lines 179-182) and Figure legend (page 26, lines 541) to indicate that the resting pressure gradient was measured.

Comment 4: The language is acceptable, but there are some grammatical or phrasal mistakes that should be improved.

Response: Thank you for your advice. We had a professional native English editor proofread the revised manuscript.

BMC Cardiovascular Disorders operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review.
system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Roberto Spoladore (Reviewer 1): Milan, June 24th 2019

Manuscript No. BCAR-D-19-00139R2

The manuscript is aimed to assess the hemodynamic features of patients with HOCM who used the bisoprolol transdermal patch during perioperative care for non-cardiac surgery. Authors concluded that bisoprolol transdermal patch could be an alternate treatment option for HOCM because the hemodynamic features of these patients did not change significantly after switching to patch therapy.

We really appreciate your very helpful and detailed comments, to which we have provided the following responses.

Comments

Comment 1: A control group with oral betablocker is lacking.

Response: Indeed, the lack of a control group with oral β-blocker was one of the limitations of our study. However, because of the single-center study design, the number of cases was limited and we could not perform a comparison with oral bisoprolol therapy in our study.

Hence, we have addressed this study limitation as follows (page 14, lines 317-319).

“First, because of the single-center study design, the number of cases was limited, and a comparison of transdermal patch therapy and standard oral bisoprolol therapy was not performed in our study.”

Comment 2: Please, provide some details about the kinetic of bisoprolol transdermal patch. In particular, specify whether the patch must be changed every day or not.

Response: The patches were applied once a day to the chest, upper back, or upper arm, and we have stated this in the Methods (page 8, lines 165). Additionally, the patch should be changed every day. Below is a table showing the kinetic parameters between the bisoprolol transdermal patch and oral tablet of bisoprolol fumarate.

Table. Kinetic parameters between the bisoprolol transdermal patch and oral tablet of bisoprolol fumarate
<table>
<thead>
<tr>
<th>Drug Formulation</th>
<th>Cmax (ng/mL)</th>
<th>C24 (ng/mL)</th>
<th>AUC72 (ng•h/mL)</th>
<th>AUC∞ (ng•h/mL)</th>
<th>tmax (h)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-mg bisoprolol transdermal patch</td>
<td>11.717±4.759</td>
<td>6.793±1.837</td>
<td>330.42±102.53</td>
<td>354.02±102.06</td>
<td>11.1±2.3</td>
<td>18.06±3.41</td>
</tr>
<tr>
<td>5-mg oral tablet of bisoprolol fumarate</td>
<td>25.93±3.79</td>
<td>4.929±0.910</td>
<td>339.92±52.92</td>
<td>371.12±59.46</td>
<td>2.6±0.7</td>
<td>9.80±0.75</td>
</tr>
</tbody>
</table>

References:


Comment 3: Which is the precise timing of drug switching before non-cardiac surgery?

Response: The trough value at 96 hours after starting bisoprolol transdermal patch administration was constant, and it reached a steady state. Therefore, we recommend that the drug be switched at more than 96 hours before non-cardiac surgery.

We have included this information in the Discussion because the precise timing of drug switching is very important during perioperative care of non-cardiac surgery in patients with hypertrophic obstructive cardiomyopathy (page 12, lines 274-276).
References:


Comment 4: Which is the precise timing of LVOT and mid-ventricular obstruction assessment after drug switching and before non-cardiac surgery?

Response: As in our response to your comment 3, the trough value at 96 hours after starting bisoprolol transdermal patch administration was constant, and it reached a steady state. Therefore, we recommend that physicians measure the pressure gradient at more than 96 hours after drug switching when they assess the LVOT and mid-ventricular obstruction. We have stated this in the Discussion (page 12, lines 276-278).

Comment 5: Which protocol of stress echocardiography was applied in order to assess the dynamic LVOT obstruction? (page 7, line 154).

Response: Our laboratory staff performed stress echocardiography using supine bicycle ergometry based on a modified protocol, which is described in a previous study (Park TH, Tayan N, Takeda K, Jeon HK, Quinones MA, Zoghbi WA. Supine bicycle echocardiography improved diagnostic accuracy and physiologic assessment of coronary artery disease with the incorporation of intermediate stages of exercise. J Am Coll Cardiol. 2007;50:1857-63.).

A symptom-limited supine bicycle protocol started at a workload of 25 watts and increased by 25-watt increments every 3 minutes until an endpoint was achieved. We were able to evaluate the pressure gradient continuously.

We have stated this in the Discussion (page 7, lines 157-161).

Comment 6: Which are the hemodynamic details during non-cardiac surgery?

Response: We also reviewed the anesthetic record during non-cardiac surgery. Although 1 case of symptomatic hypotension occurred at the time of induction of anesthesia, which immediately improved after appropriate infusion, there were no cases of uncontrolled shock and complications of heart failure and fatal arrhythmia.
We have stated this in the Methods (page 8-9, lines 185-188) and Results (page 9, lines 244-246).

Comment 7: Only one patient was included in the study with a baseline relatively high dose of oral bisoprolol (7.5 mg/day). It would be interesting to study a larger population taking higher doses of oral betablocker.

Response: We agree that it would be interesting to study patients taking higher doses of oral bisoprolol. We will perform a study with a larger number of patients to assess high doses of oral bisoprolol in HOCM in the future. We have mentioned this in the Discussion of the revised manuscript (page 12, lines 271-273).

Comment 8: How was performed the ventricular arrhythmias assessment in patients without an implanted defibrillator?

Response: All patients in the present study were assessed by continuous ECG monitoring during the perioperative period, and ventricular tachycardia and ventricular fibrillation were monitored. We have mentioned this information in the Methods of the manuscript (page 9, lines 186-188).

George Makavos, PhD (Reviewer 2):

Comment 1: "Bisoprolol Transdermal Patch for Perioperative Care of Non-cardiac Surgery in Patients with Hypertrophic Obstructive Cardiomyopathy".

Interesting and innovative study regarding transdermal administration of bisoprolol during Non-cardiac surgery.

Results in terms of hemodynamic and echocardiographic parameters and safety before switch from oral to transdermal or de novo administration of transdermal bisoprolol are adequately addressed.

I suggest that the authors will proceed with a prospective study and with an extended number of patients included, to assess transdermal bisoprolol in HOCM in the future.

Response: We really appreciate your helpful and encouraging comments. We plan to perform a prospective study to compare oral bisoprolol and the bisoprolol transdermal patch. We have mentioned this in the Conclusion of the revised manuscript (page 15, lines 333-334).