**Author’s response to reviews**

**Title:** Premedication with intranasal dexmedetomidine decreases barbiturate requirement in pediatric patients sedated for magnetic resonance imaging: a retrospective study

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**Author’s response to reviews:**

Dear Prof. Szarpak,

Thank you very much for your letter of November 26. We have now undertaken a substantial revision of the work and hope that it could be considered for publication in BMC Anesthesiology. We have done the requested changes, and hope that these will satisfy the Reviewers. We also explained why we consider this study useful and important in pediatric anesthesiology. Please, find enclosed our detailed responses to the enumerated comments of the Reviewers’ and one copy of the revised manuscript containing marked changes that have been made to the original manuscript.

Yours Sincerely,

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RESPONSE LETTER TO THE EDITOR

BANE-D-18-00500R1 Premedication with intranasal dexmedetomidine decreases barbiturate requirement in pediatric patients sedated for magnetic resonance imaging: a retrospective study

We thank the Editor and the Reviewers for their comments. Here are the comments followed by our responses:

Editor

Please include a cover letter with a point-by-point response to the comments, describing any additional experiments that were carried out and including a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.

Please also ensure that your revised manuscript conforms to the journal style, which can be found at the Submission Guidelines on the journal homepage.

A decision will be made once we have received your revised manuscript, which we expect by 26 Dec 2018.

Our response:

We thank the Editor for His comments and the possibility to response to the comments. We have responded all comments and highlighted all changes made in our manuscript with red colour. After revision, we ensured that the revised manuscript conforms to the journal style.
Reviewer #1

I reviewed with interest this article, comments are following:

1. The effects of intra-nasal dexmedetomidine in paediatric population either as a solo agent or in combination with other sedatives had been extensively reported before.

Our response:

We thank the Reviewer for a careful review of our manuscript. We agree with the Reviewer that the effects of intranasal dexmedetomidine on sedation of pediatric patients has been reported quite extensively. However, our aim was to investigate the effect of intranasal dexmedetomidine premedication on the need of additional sedation with barbiturates. There are few reports on the effect of dexmedetomidine on propofol requirements in pediatric MRI sedation, but no reports in regard to the barbiturates. Many institutions around the world still use thiopental and other barbiturates to sedate pediatric patients for MRI, and as barbiturates have an array of complications, we consider it important to study the effect of dexmedetomidine on barbiturate requirement. We have highlighted the lack of publications in this respect and revised our text in Introduction (in italics, page 3, line 23):

"In adults, dexmedetomidine reduced the dose of thiopental needed for sedation [14,22], but to our knowledge there are no previous reports on the effect of dexmedetomidine on the need of barbiturates in sedation of pediatric patients."

2. Methods: I miss any sedation scale used either before, during or after the procedure

Our response:

We thank the Reviewer for pointing out this shortcoming in our manuscript. Our practice is to sedate the pediatric patients undergoing MRI to MOAA/S (Modified Observer’s Assesment of Alertness/Sedation Scale) –level between 1 and 3. We have now added the following text to Methods (in italics, page 6, line 9):
“The decision to administer thiopental as well as the selection of the individual dose of thiopental was determined by the anesthetist in charge of the patient during the MRI procedure, and was based on the MOAA/S (Modified Observer’s Assessment of Alertness/Sedation Scale). The aim during the sedation was to keep the MOAA/S-level of the patients between 1 and 3.”

3. Methods: dexmedetomidine frequently cause hypotension, I miss any blood pressure assessment during this trial

Our response:

We agree with the Reviewer, that there are some concerns on the sympatholytic effect caused by dexmedetomidine. However, the effect of dexmedetomidine on mean arterial blood pressure levels of pediatric patients has been widely studied and it has been shown that intranasal dosages of 3 µg/kg do not cause clinically significant hypotension or hypoperfusion (Li BL et al., Paediatr Anaesth. 2015;25:891-6). Instead, hypertension may result, especially when higher dosages of dexmedetomidine are used in pediatric patients sedated for MRI. Still, a previous study with over 3500 pediatric patients showed that the incidence of hypertension is low (Mason KP et al., Paediatr Anaesth. 2010;20:516-23).

Furthermore, the sedation with dexmedetomidine keeps patients arousable and non-invasive blood pressure cuff pressure may waken patients up, which is why we do not routinely measure blood pressure in pediatric ASA 1-2 patients undergoing MRI. We measure pulse oximetry and heart rate in all patients undergoing MRI, and blood pressure when necessary. This practise has been previously described in pediatric patients undergoing MRI (Lawson GR 2000, Arch Dis Child. 2000;82:150-3, Delgado J et al., Pediatr Radiol. 2015;45:108-14; Atalay YO et al., Saudi J. Anaesth. 2017;11:185-9). We have added the following text to the Discussion (in italics, page 10, line 19):

“… induced by alpha-2-agonists may cause hypertensive crisis among pediatric patients [29-30]. However patients sedated with dexmedetomidine and furthermore receiving other sedatives must be carefully monitored for adverse events such as bradycardia. Blood pressure was not measured routinely in the patients included in our study, and was thus not included in the analysis. However, the effect of dexmedetomidine on mean arterial blood pressure levels of pediatric patients has been widely studied and it has been shown that intranasal dosages of 3 µg/kg do not cause clinically significant hypotension or hypoperfusion [13]. Higher dosages of
dexmedetomidine may cause hypertension in pediatric patients sedated for MRI, but in a previous study with over 3500 pediatric patients the incidence of hypertension was low [29].”

4. Methods: the combination between dexmedetomidine as a premedication and barbiturates will affect the post procedure recovery time, there is no assessment of post procedure sleep time

Our response:

We did not assess the post procedure sleep time, since most patients in both groups were alert immediately after MRI before transfer to PACU. We did, however, measure the time to discharge, which also includes the time of recovery. We have explained this in the Methods as follows (in italics, page 6, line 21):

“Patients fulfilled discharge criteria when they were able to drink and eat. For safety and ethical reasons all patients were observed at least 2 hours after the end of MRI. Time to discharge from the MRI unit was defined as the period of time between the end of the MRI procedure and the time when fulfilling the discharge criteria. Clock times were obtained from the hospital’s patient information system.”

and in The Discussion as follows (in italics, page 11, line 7):

“There was no statistically significant difference in time to discharge between two groups. For safety and ethical reasons all patients were observed at least 2 h after the end of MRI, despite all patients were alert soon after the end of MRI.”

5. Methods: there is no proper assessment of apnoea that may occur in the dex group.

Our response:

We agree with the Reviewer, that vital parameters should be monitored and have now revised the text in this regard to clarify this issue. It should be pointed out that many previous articles have established that dexmedetomidine does not reduce respiratory rate or increase the risk for hypercapnia, and thus does not increase the risk for apnoea. In our unit the threshold to administer supplemental oxygen is SpO2 < 94% for patients undergoing MRI under sedation. We have added text to Methods to describe our practice as follows (in italics, page 6, line 17):
“The decision to deliver supplemental oxygen was based on SpO2 levels lower than 94%. Oxygen was delivered with the “blow by” method, which is commonly used in sedated spontaneously breathing children [26], with a flow of 4 to 6 l/min.”

6. Methods: what is the maximum dose of dexmedetomidine used?

Our response:

As described in the Methods (page 6, line 21), all patients in the DEX group received 3 µg/kg of dexmedetomidine intranasally, but the individual dose was rounded to the nearest ten micrograms to facilitate dosing. Highest dose of dexmedetomidine was 110 µg in two subjects weighing 37 and 38 kg. We added median and range of dexmedetomidine to Results section as follows (in italics, page 8, line 7):

“… and a mean body-mass index (BMI) of 16.5 (2.2) kg/m2, and the THIO patients had a mean (SD) age of 4.06 (2.39) years and a mean BMI of 16.5 (1.8) kg/m2. The median (range) dose of dexmedetomidine was 50 (20-110) µg.

Reviewer #2

1. The authors have attempted to do a study to assess the decrease in the dose of Thiopental with the use of intranasal Dexmedetomidine which is very well done overall, and presents a novel yet effective measure to reduce the need for Thiopental which is associated with its own array of complications.

Our response:

We thank the Reviewer for these kind comments and for a careful review of our manuscript. The manuscript has not been changed due to this comment.
2. The primary outcome is statistically significant, and conclusions arrived at are very appropriate and may be significant. However, with regards to secondary outcomes- although statistically significant change in O2 supplementation between the groups is present, the indications for supplementation of O2 is not clearly well defined, and if the given median range of O2 saturations are above > 94% in both groups, it is unclear to me why the group not on Dexmedetomidine received so much supplemental oxygen.

Our response:

We agree with the reviewer and have now revised the text to clarify this issue. In our unit the threshold to administer supplemental oxygen for patients undergoing MRI under sedation is SpO2 < 94 %. We have added this explanation to methods section as follows (in italics, page 6, line 17):

“The decision to deliver supplemental oxygen was based on SpO2 levels lower than 94 %. Oxygen was delivered with the “blow by” method, which is commonly used in sedated spontaneously breathing children [26], with a flow of 4 to 6 l/min."

The SpO2 level given in results section is what has been measured after administration of supplemental oxygen. We have added this explanation to Results section as follows (in italics, page 8, line 23):

“The median (IQR) of the lowest observed peripheral oxygen saturation reading was 97 (95-97) % in the DEX group compared to 96 (94-97) % in the THIO group (P < 0.001). This analysis did not take into account the use of supplemental oxygen, but the reported values are after possible oxygen administration.”

3. Also, the reason why times varied for duration of MRI should be elaborated on.

Our response:

Indications for MRI scan varied in our patient group which partly explain the variability in the time of MRI. Furthermore in some occasions the sedation was not sufficient and some scans were repeated after additional doses of thiopental were administered to complete the MRI. Due
to these issues we cannot draw any conclusions about the time of MRI, but we have added the following text to Discussion (in italics, page 11, line 3):

“Despite all imaging were performed with same Siemens 1.5 T MRI scanner, there has been an software update of the scanner in year 2017, which may have reduced the length of head MRI. Indications for MRI scan varied in our patient group which partly explain the variability in the time of MRI. Furthermore in some occasions the sedation was not sufficient and some scans were repeated after additional doses of thiopental were administered to complete the MRI. Thus we cannot draw any conclusions that use of dexmedetomidine as premedication would reduce the length of MRI.”

4. Conclusions are appropriate except for the secondary outcomes.

Our response:

We thank the Reviewer for this comment. Although not specified, which secondary conclusions are inappropriate, we have checked our Results and Discussion again and have further addressed some secondary outcomes (see responses to comments 2 and 3).

We consider that our conclusions regarding the secondary outcomes are modest and based on the results. Therefore, we suggest that the Conclusions should not be changed due to this comment.

References added to the manuscript