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Anesthesiology and Pain Medicine
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Peer Review Report for "The Effect of Dexmedetomidine and Esmolol on Early Postoperative Cognitive Dysfunction After Middle Ear Surgery Under Hypotensive Technique: A Comparative, Randomized, Double-blind Study"

Author(s): Mahmoud Hussein Bahr, Doaa Abu Elkassim Rashwan, Samaa A Kasem

Review Timeline:

Submit Date:	22 Jul 2020
Revised Date:	12 Sep 2020
Accepted Date:	6 Oct 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Ebrahim Espahbodi: Reviewer | **Revision** (0) — 9 Aug 2020

Dear AE,
Is only 2% Sufflurane sufficient to maintain anesthesia?
Thanks.

REFEREE: Reviewer | **Revision** (0) — 20 Aug 2020

Dear AE,
Comments for the authors:
1- Level of education and socio-economic status are important factors that affected MMES test and in this article, these factors have not been considered.
2- MMES test and when it was meaningful for diagnosis of POCD must be explained.
3- How many scores should be reduced to make sense for distinguish of POCD?
4- This test in mild cognitive disorders and mild Alzheimer not very accurate.
5- The references, are not usually written in methods part.
6- Bleeding score should not be written in Demographic table.

7- Recovery of anesthesia: Aldert Score>8, but you said score>7, and in addition performing the test, immediately after recovery of anesthesia(MMES 1) is not very accurate.
8- Tables 2, 3 are unclear: table 2 with any significant different between two group but in table 3 at once, significant difference between two groups. MMES test is a diagnostic test for POCD, with a specified reduction in score, but in this article is unknown.
9- Did you have any complication of Dex. Especially bradycardia that need to treatment?
10- Language of article is not smooth and fluent. Some of sentences are unclear, for example : description of range of MMES in methods part, or extubation in recovery and etc.
THANKS

Ali Khatibi: Reviewer | **Revision (0)** 5 Sep 2020

Dear AE,
I read this article and have some questions from the authors:
1. As we know esmolol is a beta-blocker drug. dexmedetomidine is an alpha 2 agonist with analgesic and sedative effects.
while both drugs may reduce heart rate, but esmolol is not as effective as DEx in reducing blood pressure and inducing controlled hypotension. so how have you compared these two drugs in terms of controlled hypotension.? on the other hand what was your rescue therapy in case of any bradycardia(HR less than 50) or exaggerated hypotension(MAP less than 60)?
2. dexmedetomidin has analgesic effects while esmolol is not analgesic. the analgesic effects of dexmedetomidine will reduce hypnotic and analgesic drugs used during general anesthesia, so these patients need less sevoflurane for maintenance of anesthesia in comparison to the esmolol group . why didn't you consider this effect in your study?
Thanks.

REFEREE: Associate Editor | **Revision (0)** 6 Sep 2020

Dear EIC,
Based on reviewers' comments this manuscript needs some corrections. Also, suggest to author to consider belo below references:
- Imani F, Rahimzadeh P, Khademi H, Narimani Zamanabadi M, Sadegi K, et al. Comparison of Transforaminal Triamcinolone and Dexmedetomidine in Radicular Low-Back Pain. Anesth Pain Med. 2019;9(5):e96117.
- Imani F, Rahimzadeh P, Faiz H, Nowruzina S, Shakeri A, Ghahremani M. Comparison of the Post-Caesarean Analgesic Effect of Adding Dexmedetomidine to Paracetamol and Ketorolac: A Randomized Clinical Trial, Anesth Pain Med. 2018;8(5):e85311.
- Poorzamany Nejat Kermany M, Dahi M, Yamini Sharif R, Radpay B. Comparison of the Effects of Dexmedetomidine and Remifentanil on Cognition State After Cataract Surgery, Anesth Pain Med. 2016 ; 6(3):e33448.
Final decision: Major revision
Regards

REFEREE: EIC | **Revision (0)** 6 Sep 2020

Dear Author,

Your article is reviewed by the reviewers carefully. According to their comments, this document needs major revision. Please follow their comments as requested.

Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reviewer 1:
I read your article and have some questions:
1.as we know esmolol is a beta blocker drug . dexmedetomidin is an alpha 2 agonist with analgesic and sedative effects.while both drugs may reduce heart rate , but esmolol is not as effective as DEx in reducing blood pressure and inducing controlled hypotension. so how have you compared these two drugs in terms of controlled hypotension.? on the other hand what was your rescue therapy in case of any bradycardia(HR less than 50) or exaggerated hypotension(MAP less than 60)?

- Esmolol (an ultrashort acting selective B1 adrenergic antagonist) decreases the blood pressure and heart rate .It has rapid onset of action of bolus i.v. injection and infusion with gradual recovery of arterial blood pressure to the pre infusion level without rebound hypertension after discontinuation of infusion. Dexmedetomidine has central and peripheral sympatholytic actions which are mediated by α_2 adrenergic receptor which decreases the arterial blood pressure, heart rate, cardiac output and norepinephrine release. In this study we used esmolol and dexmedetomidine as rate control agents more than hypotensive agents.*Also previous studies compared between esmolol and dexmedetomidine as adjuvants during hypotensive anesthesia regarding their efficacy to control the blood pressure and to optimize the surgical field , and we found in the previously published literature by **Celebi et al that using esmolol to induce controlled hypotension was associated with POCD and since dexmedetomidine was reported to have a neuroprotective effect so we hypothesize that using dexmedetomidine as an adjuvant during hypotensive anesthesia may reduce the incidence of early POCD when compared to esmolol.

*A Das, S Chhaule, S Bhattacharya, SR Basunia,[1] T Mitra,[2] PS Halder, S Chattopadhyay, and SK Mandal.Controlled hypotension in day care functional endoscopic sinus surgery: A comparison between esmolol and dexmedetomidine: prospective, double-blind, and randomized studySaudi J Anaesth. 2016 Jul-Sep; 10(3): 276–282.)

**(Celebi N, Artukoglu F, Dal D, Saricaoglu F, Celiker V, Aypar U. Effect of hypotensive anesthesia on cognitive functions; a comparison of esmolol and remifentanyl during tympanoplasty. *Saudi Med J* 2007; 28: 1357–61. PMID:17768460.)

- Our rescue therapy in case of bradycardia or exaggerated hypotension was to discontinue infusion of esmolol and dexmedetomidine , and to administer ephedrine in 5 mg increments if the MAP decreased to 55 mmHg or less, and 0.5 mg i.v. atropine to the patients who developed bradycardia (heart rate <60 beat/minute), and to exclude those patients from the study but *non of the patients had bradycardia*

or exaggerated hypotension (figure2 and3)

2. dexmedetomidin has analgesic effects while esmolol is not analgesic. the analgesic effects of dexmedetomidin will reduce hypnotic and analgesic drugs used during general anesthesia , so these patients need less sevoflurane for maintenance of anesthesia in comparison to esmolol group . why didn't you consider this effect in your study ?

-We considered this and the sevoflurane concentration was observed during surgery, but recording the sevoflurane concentration was not one of the primary or secondary outcomes for this study .

Reviewer 2:
Dear authors
Is only 2% Sufflurane sufficient to maintain anesthesia?

- when using esmolol and dexmedetomidine to reach the target MAP(55-65mmHg), it was not required to increase the sevoflurane concentration)and this was the benefit of using these adjuvants during controlled hypotension to avoid increasing the dose of inhalational anaesthetic and to provide an effective hypotensive anesthesia and to improved visibility of the surgical site. Since increasing the dose of inhalational anesthetics to produce controlled hypotensive anesthesia, affects the brain function including the cerebral blood flow and metabolism .Also fentanyl 2migrogram/kg was administrated during induction of anaesthesia and the mild to moderate painful surgery make the change in sevoflurane level mild (2-2.5%)

Reviewer 3:
Dear Author:
1- Level of education and socio-economic status are important factors that affected MMES test and in this article, these factors have not been considered.

-All the patients of both groups were educated (secondary school or higher), non-educated patients and patients with high educational professional degrees were excluded for the accuracy of the MMSE.The socio-economic level was also comparable.

2- MMES test and when it was meaningful for diagnosis of POCD must be explained.

- in this study the Mini-Mental State Examination (MMSE) (Appendix 1) was selected because it is easily applicable, highly valid, and reliable and is the most commonly used composite measure. I

Also in the study of POCD the optimum timing of assessments is not established but POCD assessments that occur in the immediate postoperative period are important for elucidating the relationship between POCD and delirium.
So depending in the hypothesis of this study that dexmedetomidine may have a neuroprotective effect(as reported by previous literature *.**,***) the test was applied early postoperatively and the results of the study showed that the number and percentages of the patients in the dexmedetomidine group who had decreased cognitive functions are less than those in the esmolol group

* Kuhmonen J, Pokorny´ J, Miettinen R, et al. Neuroprotective effects of dexmedetomidine in the gerbil hippocampus after transient global ischemia. *Anesthesiology* 1997; 87: 371–377.

**Dahmani S, Paris A, Jannier V, Hein L, Rouelle D, Scholz J, Gressens P, Mantz J. Dexmedetomidine increases hippocampal phosphorylated extracellular signal-regulated protein kinase 1 and 2 content by an alpha 2-adrenoceptor-independent mechanism: evidence for the involvement of imidazoline I1 receptors. *Anesthesiology* 2008; 108: 457–66.

***Sato K, Kimura T, Nishikawa T, Tobe Y and Masaki Y. Neuroprotective effects of a combination of dexmedetomidine and hypothermia after incomplete cerebral ischemia in rats. *ActaAnaesthesiol Scand* 2010; 54:377-382. DOI.10.1111/j.1399-6576.2009.02139.x

3- How many scores should be reduced to make sense for distinguish of POCD?

- the Mini-Mental State Examination (MMSE) is the most commonly used composite measure ,also the debate is whether to use composite measures and composite scores to diagnose POCD.

4- This test in mild cognitive disorders and mild AIzheimer not very accurate.

-The test was applied preoperatively and all patients were educated, so none of the patients had preoperative decreased cognitive function , all patients were ASA I, also the mean of the age was 33.1 ± 7.3 *for the patients in the esmolol group versus* 31.9 ± 8.1 *for the patients in the dexmedetomidine group* ,it was also reported that the time interval at which a diagnosis of POCD holds the greatest clinical significance has not been determined,

5- The references, are not usually written in methods part.

- these are the references for the doses and the used scores,

6- Bleeding score should not be written in Demographic table.

-this will be mentioned separately

7- Recovery of anesthesia: Aldert Score>8, but you said score>7, and in addition performing the test, immediately after recovery of anesthesia(MMES 1) is not very accurate.

- When the *Modified Aldrete Score was ≥7 the patients were awake, **but discharging from the post anesthesia recovery unit to the ward was considered when the sore ≥9 (phase I recovery)and because the primary outcome of this study was to examine the effect of dexmedetomidine versus esmolol on the early postoperative cognitive dysfunction , so the test was applied at 1 hour postoperative not immediately postoperatively (This reading was considered as (MMSE1) , and the test was repeated at 6 hours (MMSE6) and 24 hours (MMSE24) postoperatively.

*Aldrete, JA (February 1995). "The post-anesthesia recovery score revisited". *Journal of Clinical Anesthesia*. **7** (1): 89–91. doi:10.1016/0952-8180(94)00001-k

8- Table2,3 are unclear: table 2 with any significant different between two group but in table 3 at once, significant difference between two groups. MMES test is a diagnostic test for POCD, with a specified reduction in score, but in this article is unknown.

- this comment is not clear, kindly explain it more?

Table 2. The Mini-Mental State Examination(MMSE) score (preoperative and postoperative)

	Esmolol group (n = 29)	Dexmedetomidine group (n = 29)	p value
MMSE preoperative	27 (24-30)	27 (24-30)	0.880
MMSE 1hpost	26 (23-30)	27 (23-30)	0.263
MMSE 6h post	27 (24-30)	27 (24-30)	0.385
MMSE 24h post	28 (24-30)	28 (24-30)	0.658

Values are presented as median (range), P value< 0.05 is considered statistically significant.

Table 3. The incidence of Post-Operative Cognitive Dysfunction MMSE 23- 24

	Esmolol group (n = 29)	Dexmedetomidine group (n = 29)	p value
1h postoperative	12 (41.37 %)	3(10.34%)	*0.016*

6h postoperative	10(34.48%)	2(6.89%)	*0.023*
24h postoperative	7(24.13%)	1(3.44%)	*0.022*

Values are described as number (percentages), P value< 0.05 is considered statistically significant.

The median and range of MMSE score were nearly comparable between the two groups at 1,6 and 24 hours postoperatively;(p >0.05);(Table 2), but since a decrease of 2 or more of MMSE was recorded as cognitive function decline and a score lower than 24 was recorded as cognitive impairment, so based on this knowledge we calculated the incidence **of Post-Operative Cognitive Dysfunction at 1,6 and 24 hours postoperative in term of number and percentage of the patients** and the results are presented in table 3 which showed that although there was no significant difference in the median and range of MMSE between both groups but there was significant difference (p value less than 0.05) when calculating the number and percentage of the patients who had MMSE 23- 24 at different time postoperatively for the esmolol group more than dexmedetomidine group , supporting the hypothesis that dexmedetomidine has a neuroprotective effect.

9- Did you have any complication of Dex. Especially bradycardia that need to treatment?

-Non of the patient had bradycardia in both groups (figure 3),no other complications related to dexmedetomidine (as delayed recovery) was observed.

10- Language of article is not smooth and fluent. Some of sentences are unclear, for example : description of range of MMES in methods part, or extubation in recovery and etc.

-This will be adjusted, thanks

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) — 6 Oct 2020

Dear AE,
I read with interest this revised manuscript and the majority of requested items were corrected.
Sincerely

REFEREE: Associate Editor | **Revision** (1) — 6 Oct 2020

Dear EIC,
Based on reviewers' comments this revision is acceptable for publishing.
Regards

REFEREE: EIC | **Revision** (1) — 6 Oct 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.