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OPEN PEER REVIEW

Comparison of the Preemptive/Preventive Effect of Dexmedetomidine and Ketorolac on Post-operative Pain of Appendectomy Patients: A Randomized Clinical Trial

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About this report

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1 Original submission

5 comments · 23 Mar 2024 – 27 Apr 2024

Referee 1 Reviewer

MAJOR REVISION 23 Mar 2024

Hello, Authors.
Thank you for contributing to the journal.
I read the article and have some queries and thoughts.
1. What is this study's key novelty? Dexmedetomidine and ketorolac belong to two different classes of analgesics with different pharmacokinetics. Why have you compared them in your study?
2. The objective section of the abstract looks like a methods section. Correct it and make the background and objective sections of the abstract concise and specific.
3. The conclusion section of the abstract is inadequate. Briefly compare the outcomes of the drugs used in the study.
4. The abstract is too imperfect and requires further revision and editing.
5. The introduction is useful; however, it might be briefer. Consider reducing background information to make it more focused and mention why you have chosen these two drugs in your study.
6. In the methods section, how will you make sure that the patient receiving the drug in syringe A1 before induction will receive only the drug in syringe A2 after induction? Please elaborate in the methods section.
7. In the methods section, specify the total fentanyl PCA dose limit for a particular period of time.
8. The statistical analysis section requires further information on the exact statistical tests employed for each comparison.
9. The results section must be restructured and better explained. Also provide tables for the variables for which the p-values are significant.
10. The discussion should systematically and clearly explain the study findings and compare them with those of other similar studies. Do not repeat findings in the discussion more than once. Make it more concise and specific.
11. The second paragraph of the discussion, from line 297 to line 308, needs more explanation. Make it more presentable and easier to understand.
12. References should not be more than 5 years old.

Ali Khatibi Reviewer

ACCEPT 27 Apr 2024

dear authors
Thank you for your valuable study.
Why did you record and analyze the body temperature of your patients in this study, and why didn't you mention higher temperatures in the group of patients receiving dexmedetomidine in the discussion of your article?

Referee 2 Reviewer

MINOR REVISION 27 Apr 2024

Dear AE,
I was pleased to have the opportunity to review the manuscript entitled 'Comparison of the preemptive/preventive effect of Dexmedetomidine and ketorolac on post-operative pain of appendectomized patients: A randomized clinical trial'. This research article presents a well-conducted randomized clinical trial

comparing Dexmedetomidine and ketorolac for preemptive/preventive analgesia in appendectomy patients. The study methodology is robust, and the results are clearly presented and discussed in the context of existing literature. However, the authors could enhance the manuscript by providing more detailed information on adverse events and addressing the concerns below:

• Some sentences lack references. All sentences quoted from other articles must have references at the end. For example, the following sentences:

"In rat models, the dexmedetomidine systemic administration leads to α2-adrenoceptor stimulation that possibly facilitates inhibitory synaptic reactions in the superficial dorsal horn for producing analgesia, which can be adjusted by activating the pontospinal noradrenergic inhibitory system. Additionally, it probably produces analgesia by showing activity at the locus coeruleus (LC) in pons."

• Introduction:

o Mention how the sample size was determined (if applicable).

• Results:

o Briefly mention if there were any missing data points.

• Discussion:

o The discussion could be strengthened by providing more in-depth analyses of potential confounding factors and alternative explanations for the observed outcomes.

Associate Editor

MAJOR REVISION 27 Apr 2024

Dear EIC,

I thank the authors and express my appreciation to the researchers. The manuscript presents valuable research. But some revisions are needed. The authors should revise it based on the reviewers' comments.

Editor-in-Chief

MAJOR REVISION 27 Apr 2024

Dear Author,

Thank you for submitting the article. It needs some revision. Please revise it based on the reviewers' and AE's comments.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewer 1:

1. What is this study's key novelty?

Reply: The novelty of this study stands on this fact that no other study, as far as we have searched, has not studied or compared these two drugs (dexmedetomidine and ketorolac) applied intravenously in a clinical trial for understanding the preemptive/preventive analgesic effects in appendectomy patients. Dexmedetomidine and ketorolac are two distinct agents with different mechanisms of action and this is another appealing fact to compare them. It has been also emphasized to use non opioid modalities preoperatively in order to have less side effects (Baboli etal. Current Problems in surgery:, July 2020).

Dexmedetomidine and ketorolac are two different class of analgesics with unlike pharmacokinetics, why you have compared them in your study?

Reply: Dexmedetomidine and ketorolac are commonly used in the perioperative anesthesia management and we wanted to know which one has a distinct preemptive/preventive effect. If we had chosen two agents with similar pharmacokinetics the results would be not be so significant.

2. The objective section of the abstract looks like methods section, correct it and make background and objective part of abstract concise and specific.

Reply: The objective and method sections of the abstract were revised and corrected.

3. The conclusion section of the abstract is inadequate. Briefly compare the outcome of drugs used in study.

Reply: The conclusion section of abstract was revised accordingly.

4. The abstract is too imperfect and requires further revision and editing.

Reply: The abstract was thoroughly revised accordingly.

5. The introduction is useful; however, it might be briefer. Consider

reducing background information to make it more focused and mention why you have chosen these two drugs in your study.

Reply: The introduction was thoroughly revised accordingly.

6. In methods, how will you make sure the patient receiving syringe A1 drug before induction will only receive syringe A2 drug after induction, please elaborate in method section.

Reply: we did not explain about this in the methods due to word content limitation but thank you for mentioning it. Each patient was randomly assigned to a group A, B or C and when this was done the package of syringes $A_{1\&2}$ or $B_{1\&2}$ or $C_{1\&2}$ was delivered to the anesthesiology resident who was informed to apply the syringes 1 and 2 in a sequential manner according to the protocol of the study. The sections of method were revised and highlighted in the text.

7. In method section, specify the total limit of fentanyl PCA dose for particular period of time.

Reply: We used an Automed 3400 PCA semi-electronic disposable pump (ACE MEDICAL ©, Bomun-ro, Seongbuk-gu, Seoul, South Korea, www.ace-medical.com). This pump does not have the specifications for hourly dose limiting mode. For this reason, we did not define a total dose limit for fentanyl. *Jung, Haesun, et al. "Effect of Fentanyl-Based Intravenous Patient-Controlled Analgesia with and without Basal Infusion on Postoperative Opioid Consumption and Opioid-Related Side Effects: A Retrospective Cohort Study." Journal of Pain Research 13 (2020): 3095.*

8. The statistical analysis section requires further information on the exact statistical tests employed for each comparison.

Reply: The statistical analysis were applied and added as requested. Page 15

9. The result section must be restructured and better explained. Show tables also for the variables for which the p-values are significant.

*Reply: T*he result section was revised accordingly.

10. The discussion should be systematic and explainable about the

study findings and clearly comparing with other similar studies. Do not repeat findings in discussion more than once. Make it more concise and specific.

Reply: The discussion section was revised accordingly.

11. Second paragraph of discussion part from line 297 to line 308 need more explanation. Make it more presentable and clearer to understand.

Reply: This discussion section was revised accordingly.

According to Joel Katz a preventive (preventive analgesia is broder definition of preemptive analgesia) analgesic can be related to an agent when the time duration of this impact is longer than the agents target effect, which has been defined by them as 5.5 times the half-life of that particular agent. This means that the process of preventive analgesia should not be a direct result of the agent's analgesic property. Overall in this study the pain intensity was significantly lower in the ketorolac group in the earlier hours after operation but was changed in the favor of the dexmedetomidine group in the later hours after surgery. This may indicate that the dexmedetomidine preventive effect at this time point is almost beyond the 5.5 times its half-life [dexmedetomidine half-life; 2-3 hours]. However, for ketorolac this did not happen. Because, 22-33 hours after the administering ketorolac [ketorolac's half-life 4-6 hours which is longer than] the VAS scores in the ketorolac group did not attenuate statistically compared to group D and C.

12. References should not be more than 5 years old
Reply: Almost all of the references were changes in confine to the context of 5 years. However, because of the novelty and concepts in a few of the references they were kept in the manuscript.

Reviewer 2:

1. why did you record and analaysed body temperature of your patients in this study and why did'nt you mention about higher temperatures in patients receiving dexmedetomidine group in discussion of your article?
Reply: thank you for your comment we added a paragraph about this in

the discussion. We searched the literature thoroughly and found controversial reports for dexmedetomidine thermal effects.

It has been stated that dexmedetomidine can cause either decreases or increases in the body temperature, even fever in some cases have been reported too. The range of temperatures have been reported in the range of 35 to 37.8 °C. In our study the temperatures in the dexmedetomidine group were higher compered to ketorolac and control group. Although different mechanisms such as drug effects on thermoregulation, drug administration-related reactions, pharmacologic drug actions, idiosyncratic responses, and hypersensitivity/ immunologic reactions have been proposed but the exact the explanation for such finding is pending to more studies.

Reviewer 3:
Dear AE,
I was pleased to have the opportunity to review the manuscript entitled 'Comparison of the preemptive/preventive effect of Dexmedetomidine and ketorolac on post-operative pain of appendectomized patients: A randomized clinical trial". This research article presents a well-conducted randomized clinical trial comparing Dexmedetomidine and ketorolac for preemptive/preventive analgesia in appendectomy patients. The study methodology is robust, and the results are clearly presented and discussed in the context of existing literature.

1. *However, the authors could enhance the manuscript by providing more detailed information on adverse events and also below concerns:*
   Reply: thank you for your comments The discussion section was revised accordingly.
   The adverse events our study were scarce but we added comments related to PONV, shivering and body temperature.

   It has been stated that dexmedetomidine can cause either decreases or increases in the body temperature, even fever in some cases have been reported too. The range of temperatures have been reported in the range of 35 to 37.8 °C. In our study the temperatures in the dexmedetomidine group were higher compered to ketorolac and control group. Although different mechanisms such as drug effects on thermoregulation, drug administration-related reactions, pharmacologic drug actions,

idiosyncratic responses, and hypersensitivity/ immunologic reactions have been proposed but the exact the explanation for such finding is pending to more studies.

It has been reported that the intraoperative infusion of dexmedetomidine can attenuate the occurrence of postoperative nausea and vomiting during recovery due to the reduced amount of opioid consumption perioperatively However, in a study in bariatric surgery patients dexmedetomidine was not associated with decreased incidence of PONV compared to the standard control group Similarly, in our study, we did not find a significant decrease in PONV in D goup compared to other groups, and despite meperidine administration for three patients in the recovery period, nausea and vomiting outcomes were almost the same. Similar results were shown by Xu et al.

2. *Introduction:*
   o Mention how sample size was determined (if applicable).

   For calculating the sample size for each group one-sided analysis of variance was used considering mean values of the VAS scores one hour after operation from a prior pilot study which were as following $\mu_1 = 2.8$, $\mu_2 = 5$, $\mu_3 = 7$ for the dexmedetomidine, ketorolac and control groups respectively. Sample size calculations was applied by taking the $\alpha = 0.01$, $\beta = 0.1$, $\sigma = \sqrt{MSE} = 2.55$. We calculated a λ from the above indices and obtained a non-central distribution χ^2 equal to 12.66 and the Δ the number of cases for each group was 15. For a possibility of drop outs we choose a number of 20 patients for each group (NCSS software).

$$\Delta = \frac{1}{\sigma^2}\sum_{i=1}^{k}(\mu_i - \bar{\mu})^2 \quad ; \quad \bar{\mu} = \frac{1}{k}\sum_{i=1}^{k}\mu_j \quad ; \quad \chi^2_{k-1}(\chi^2_{\alpha,k-1} \mid \lambda) = \beta$$

.

3. *Some sentences lack references. All sentences quoted from other articles must have references at the end of themselves.*
   for example below sentence:
   In rat models, the dexmedetomidine systemic administration leads to α2-adrenoceptor stimulation that possibly facilitates inhibitory synaptic reactions in the superficial dorsal horn for producing analgesia, which can be adjusted by activating the pontospinal noradrenergic inhibitory system. Additionally, it probably produces analgesia by showing activity at the locus coeruleus (LC) in pons.

Reply: The part was revised and almost all the references were revised and checked.

4. • *Results:*
   o Briefly mention if there were any missing data points•

Reply: The section related to sample recruitment was revised accordingly.

On the other hand, the exclusion criteria were 1) history of allergy to the prescribed medications; 2) addiction or elicited use of drugs and analgesics; 3) complicated appendicitis; 4) neurological disorders; 5) neuropathic pain; 6) treatment with analgesic or anti-inflammatory medications; 7) pregnancy or breastfeeding; 8) unwillingness to participate in the study. Fourteen patients were excluded from the 85 due to the above criteria. From the 71 patients assigned to the study groups 11 were omitted due to complicated surgery and unexpected conditions during the operation (Figure 1).

5. *Discussion:*
   o the discussion could be strengthened by providing more in-depth analyses of potential confounding factors and alternative explanations for the observed outcomes.

Reply: Many parts of the discussion had been revised as the editorial board had asked for. Some parts are as bellows:

The extenuative effect of dexmedetomidine in our study 12 and 24 hours postoperatively is in contrast to the findings of previous studies , where dexmedetomidine was shown to be most effective only until the 48th hours postoperatively (18).

The extend of tissue trauma in our study was mild to moderate, compared to the above-mentioned studies. However, we obtained favorable results in the dexmedetomidine group, which suggest that the study protocol affects the outcomes more than other variables. In line with this finding, a study by Fu et al. (34) showed that the VAS scores and outcomes were more favorable in the dexmedetomidine group.

Different mechanisms for the analgesic effects of dexmedetomidine have been stated, such as prevention of pain impulse transmission through activation of alpha-2 adrenergic receptors at the spinal level (as well as supraspinal and peripheral loci), suppression of the affective-motivational and stress factors of pain, reducing opioid-induced hyperalgesia (35), reduced activation of the sympathetic system (and subsequent attenuation of cytokines and chemokines released due to tissue damage) or inhibiting nuclear factor kappa-β activation (36), which are comparable to the peripheral action of ketorolac. Ketorolac has both central and peripheral activities, which make it a suitable analgesic agent for postoperative pain if administered intraoperatively; the efficacy is lower if administered postoperatively (37) . Although the opioid receptor activity of ketorolac has been confirmed (38), the antinociceptive activity of dexmedetomidine was superior in our study due to its longer analgesic effects within 24 hours after surgery.

2 Revision 1

3 comments · 28 Sep 2024 – 9 Nov 2024

Referee 2 Reviewer

ACCEPT 28 Sep 2024

Dear AE,

I reviewed the manuscript again. The great effort in improving the manuscript is highly appreciated.
The authors have addressed all comments.
Thank you

Associate Editor

ACCEPT 9 Nov 2024

Dear EIC,
I reviewed the manuscript again. The great effort in improving the manuscript is highly appreciated.
The authors have addressed all comments.
Thank you

Editor-in-Chief

ACCEPT 9 Nov 2024

Dear AUTHOR,
Thank you for paying attention and responding to the reviewer's comments.