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OPEN PEER REVIEW

Double-Blind, Randomized, Controlled Pilot Trial to Specify Collateral Effect and Safety of Perioperative Dexmedetomidine in Patients Undergoing Open Heart Surgery

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

4 comments · 22 Nov 2024 – 2 Dec 2024

Referee 1 Reviewer

MAJOR REVISION 22 Nov 2024

Dear Author
Thank you for this research. After reviewing it, I suggest clarifying the following points:
1-Did the patients receive any drugs except anesthetic drugs during surgery?
2-When was dexmedetomidine started: before or at induction? In some sentences, the author compared preoperative hemodynamic parameters in the dex group with those in the control group.
3-When was the administration of anesthetic drugs (dex., isoflurane, etc.) stopped?
4-What was the drug history of the patients?
5-Did you have any information on patients' FBS and lactate before surgery? They must be in the demographic table.
6-The duration of surgery should be included in the demographic table.
7- Did you measure pain and the need for analgesics in the groups?
8-The CONSORT diagram should be drawn.
9-The P-value in the demographic table was not shown.
10-Did you suggest dexmedetomidine as a sole or adjunct drug?
11-Reference No.24 is the same as Ref—no. 29.

Thank you

Referee 2 Reviewer

MAJOR REVISION 30 Nov 2024

Dear AE,
This study provides a valuable preliminary insight into the safety and efficacy of Dexmedetomidine in open-heart surgery. With a few adjustments in design and presentation, this work could form a strong foundation for larger, more definitive trials:
- Some sentences lack references, for example, the first sentence of the background.
- The study reports that recovery times were similar between the groups but does not explore other important postoperative outcomes like pain scores, delirium, or time to extubation. Dexmedetomidine has been shown to reduce postoperative delirium, improve pain control, and hasten extubation in other studies, but these critical outcomes are not evaluated here.
A detailed assessment of postoperative outcomes, including pain, delirium, extubation time, ICU stay duration, and long-term complications, would provide a more comprehensive understanding of Dex's benefits.
- The study mentions some adverse effects (e.g., hypotension, bradycardia, and tachycardia) but does not discuss the severity, duration, or management of these events in detail. The lack of granularity in adverse event reporting makes it challenging to assess the clinical relevance and safety profile of Dexmedetomidine in this setting. Detailed adverse event data, including the timeline, intervention required, and clinical impact, should be reported for better safety assessment.
- The study applies multiple statistical tests but does not address the potential for Type I errors due to repeated testing on a small sample. Repeated testing increases the likelihood of false-positive results, and the study does not mention any corrections (e.g., Bonferroni adjustment) for multiple comparisons.
Use appropriate statistical corrections and ensure the methodology is rigorous, especially for small sample

sizes.
- While the study mentions the anti-inflammatory effects of Dexmedetomidine, it does not measure inflammatory markers (e.g., C-reactive protein, IL-6): Without these measurements, it is unclear whether Dex's purported anti-inflammatory benefits contributed to the observed outcomes.
Suggestion: Please include measurements of inflammatory markers to substantiate claims of anti-inflammatory effects.

Associate Editor MAJOR REVISION 2 Dec 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 2 Dec 2024

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

2

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.

14 Dec. 2024

Dear Dr. Mahmood-Reza Alebouyeh

Editor-in-Chief, Anesthesiology and Pain Medicine

Please find our revised manuscript entitled: "**Double-blind, randomized, controlled pilot trial to specify collateral effect and safety of perioperative Dexmedetomidine in patients undergoing open heart surgery**"(**Manuscript ID: 157117**).

We would like to appreciate the reviewers for their constructive comments which helped us to improve our manuscript. We have carefully taken their comments into consideration in preparing the revised manuscript. Below we have provided our response to the comments point by point.

Thank you so much in advance for your further consideration. If I can provide you with additional information, please feel free to contact me.

Best Regards,

Ali Jabbari, and Ali Movafegh, M.D.

Ischemic disorder research center, Department of Anesthesiology and Critical Care Medicine, Golestan University of Medical Sciences, Gorgan, Iran.

Department of Anesthesiology, School of Medicine faculty, Tehran University of Medical Sciences, Tehran, Iran.

Dear reviewers,

Dear reviewers and associate editor, we would like to thank you for taking time out of your busy schedule to review our manuscript and provide your constructive comments. We have provided a point-by-point response to your concerns. Throughout the manuscript's text, all changes are highlighted in yellow. We hope that you find our responses satisfactory.

Reviewers' Comments:

Reviewer 1:
Dear Author
Thank you for this research. After reviewing it, I suggest some points that would be better to explain as follows:

1-Did the patients receive any drugs except anesthetic drugs during surgery?
According to the reviewer's comments, patients were received TNG during surgery, and some also received Millrinone and norepinephrine based on their underlying conditions.

2-When did dexmedetomidine start: before or at induction? In some sentences, the author compared preoperation hemodynamic parameters in the dex group with those in the control group.
According to the reviewer's comments, during the process of anesthetic induction, patients were administered an initial loading dose of dexmedetomidine. Following this initial administration, they continued to receive a maintenance dose of the medication to ensure effective sedation and stability throughout the duration of the procedure.

3-When was the administration of anesthetic drugs (dex., isoflurane, etc.) stopped?
According to the reviewer's comments, after the surgery and transfer to the ICU, anesthetic drugs, including dexmedetomidine, were stopped. However, some patients were given a brief dose of midazolam or morphine until it was confirmed there was no early postoperative bleeding.

4-What was the drug history of the patients?
According to the reviewer's comments, patients eligible for heart surgery often have underlying conditions like diabetes or high blood pressure, leading many to have previously received medications to manage these issues.

5-Did you have any information on patients' FBS and lactate before surgery? They must be in the demographic table.

According to the reviewer's comments, the table1 was revised and patients' baseline characteristics such as lactate level and blood sugar were reported as "**Table 1.** Patient's demographic characteristics" (page 8). But, patients' FBS not assayed.

Table 1. Patient's demographic characteristics.

Characteristic	Group		P-value
	Control (n=10)	Dex (n=10)	
Mean Age ± SD, years	58.88 ± 8.17	58.90 ± 8.02	0.995
Male/female (n)	4/6	6/4	0.371
Original surgical procedures, n (%)			
CABG	6 (60%)	8 (80%)	
CABG+AVR	0	0	
TVR+MVR	1 (10%)	0	
CABG+ASD	1 (10%)	0	
CABG+MVR	1 (10%)	0	
MVR	1 (10%)	0	
AVR	0	1 (10%)	
AVR+MVR	0	1 (10%)	
Hypertension, n (%)	9 (90%)	7 (70%)	0.582
Diabetes mellitus, n (%)	2 (20%)	6 (60)	0.170
Lactate, (mmol/L)	1.11 ± 0.42	1.34 ± 0.39	0.219
Blood sugar (BS), (mg/dL)	119.80 ± 54.65	159.30 ± 64.66	0.157
Op-time (hours)	5.846 ± 0.31	5.000 ± 0.45	0.258
Recovery Time (hours)	9.50 ± 2.12	10.80 ± 2.10	0.185

6-The duration of surgery should be included in the demographic table.
According to the reviewer's comments, it was inserted in the table 1 (above answer) as "Op-time".

7- Did you measure pain and need analgesics in groups?
According to the reviewer's comments, pain levels are recorded using a visual analogue scale (VAS) as per intensive care unit standards. Painkillers are prescribed according to protocol if the patient requests them or if the pain score exceeds 4. Typically, Apotel or NSAIDs are the first-line medications for pain management in most patients.

8-The consort diagram should be drawn.
According to the reviewer's comments, the consort diagram was added in the manuscript (page 7) as follow:

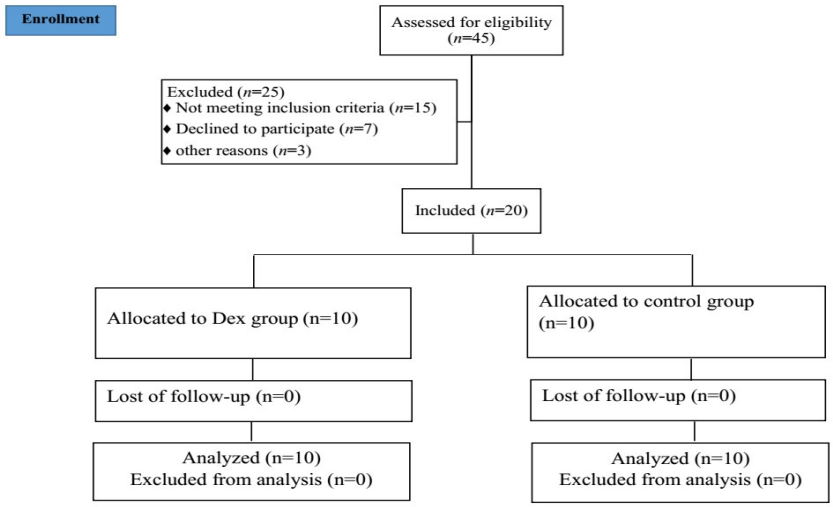


Figure 1. Consort flow chart.

9-The P-value in the demographic table was not seen.

According to the reviewer's comments, the P-value for gender, hypertension, and diabetes mellitus in the demographic table was added. In addition, for original surgical procedures, the expected and observed frequencies were small and the assumptions of the chi-square distribution were not met. Therefore, the test was not performed. For the reader's information, only the frequencies were reported.

Table 1. Patient's demographic characteristics.

Characteristic	Group		P-value
	Control (n=10)	Dex (n=10)	
Mean Age ± SD, years	58.88 ± 8.17	58.90 ± 8.02	0.995
Male/female (n)	4/6	6/4	0.371
Original surgical procedures, n (%)			
CABG	6 (60%)	8 (80%)	
CABG+AVR	0	0	
TVR+MVR	1 (10%)	0	
CABG+ASD	1 (10%)	0	
CABG+MVR	1 (10%)	0	
MVR	1 (10%)	0	
AVR	0	1 (10%)	
AVR+MVR	0	1 (10%)	
Hypertension, n (%)	9 (90%)	7 (70%)	0.582
Diabetes mellitus, n (%)	2 (20%)	6 (60)	0.170
Lactate, (mmol/L)	1.11 ± 0.42	1.34 ± 0.39	0.219
Blood sugar (BS), (mg/dL)	119.80 ± 54.65	159.30 ± 64.66	0.157
Op-time (hours)	5.846 ± 0.31	5.000 ± 0.45	0.258

Recovery Time (hours)	9.50 ± 2.12	10.80 ± 2.10	0.185

10-Did you suggest dexmedetomidine as a sole or adjunct drug?
According to the reviewer's comments, polypharmacy is a common strategy for both induction and maintenance of balanced anesthesia, especially in cardiac procedures where total intravenous anesthesia (TIVA) is necessary due to cardiopulmonary bypass. This study examines the use of Dex during anesthesia induction and in the intraoperative injection cocktail.

11-The reference No.24 is the same as Ref—no. 29.
According to the reviewer's comments, the reference section was revised and corrected. The Ref. 29 was deleted and ref.' numbers were corrected.

Thank you

Reviewer 2:
Thank you very much for inviting me to review the manuscript entitled" Double-blind, randomized, controlled pilot trial to specify collateral effect and safety of perioperative Dexmedetomidine in patients undergoing open heart surgery"
After read of this manuscript, I recommend these points.
The points:
1. There isn't new point in this study.
Thanks for this comment. Several studies have highlighted the benefits of Dex in cardiac surgery, primarily focusing on postoperative events and its analgesic and sedative roles, with no consensus on these effects. In contrast, our study offers important advantages: 1) it evaluates the efficacy and safety of Dex with fewer side effects in open heart surgery patients, 2) it explores the hemodynamic and respiratory stability effects of Dex during cardiac surgery, 3) it compares the sympatholytic and α2-adrenergic effects of Dex to anesthetic drugs, as indicated by hemodynamic stability and lactate reduction, and 4) it broadens the clinical applications of dexmedetomidine.

2. The number of words in the abstract should be adjusted according to the instruction for authors (250 words).
According to the reviewer's comments, the abstract was revised as follows:

"**Background:** This study was performed to assess the collateral effect and safety of dexmedetomidine (Dex) during and one day after surgery in Iranian patients who underwent open heart surgery to expand the clinical applications of Dex in Iran. **Methods:** This pilot study was conducted in Gorgan, Golestan province, Iran in 2024. Both male and female participants with open heart surgery were randomly assigned to either the Dex group (n=10), receiving 0.5 µg/kg/h along with standard anesthesia management or control groups (n=10). The primary outcome was to evaluate the percentage of patients with adverse effects. The secondary outcomes were the stability of hemodynamic and respiratory parameters, arrhythmia incidence and biological changes, which were assessed during and 24-hours after surgery. **Results:** Out of 45 participants, 20 were enrolled and analyzed. The comparison between groups showed that observed adverse effects in the control group (4 patients) were higher than Dex group (1 patient), common events were hypotension, bradycardia and tachycardia. The biological markers (lactate and blood glucose) increased in both groups, and the control group showed more increase in both level of lactate and blood glucose; namely p=0.012 and p=0.009, respectively and p=0.017 and p=0.093, respectively, in the Dex group. In addition, there were no significant differences in hemodynamic and respiratory markers between the groups (P > 0.05); but, Dex improved and persevered more in hemodynamic and repository stability. **Conclusion:** Adjunctive adding Dex to anesthesia protocol was safe without any adverse collateral effect and promising role in improving cardiac function in patients undergoing open-heart surgery."

3. There isn't consort diagram in the text.
According to the reviewer's comments, the consort diagram was added in the manuscript (page 7) as follow:

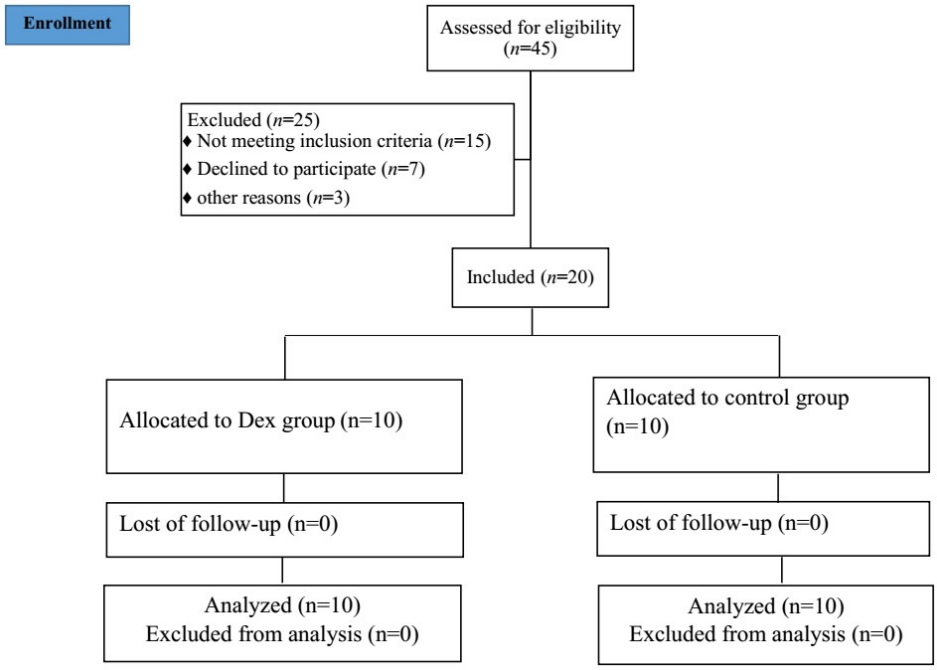


Figure 1. Consort flow chart.

4. The sample size is very small and the variety of patients is great, it may distort the results.

According to the reviewer's comments, in a clinical trial conducted in Japan to investigate the efficacy and safety of dexmedetomidine for procedural sedation in patients receiving local anesthesia outside the intensive care unit, bradycardia was the most important adverse event of this drug, which was reported significantly more frequently in the dexmedetomidine group than in the control group. In the study by Zhai et al., changes in heart rate were examined immediately after sternal closure, 4, 12, and 24 hours after surgery. Considering the mean (standard deviation) heart rate immediately after sternal closure of 59.83 (3.66) beats per minute in the dexmedetomidine group and 68.06 (4.49) beats per minute in the placebo group, a sample size of 6 patients in each group was required to detect between-group differences at a two-sided significance level of 5% with 80% power based on the t-test. Using G Power software, the sample size for heart rate changes 4 hours after surgery was also calculated, and their maximum was selected as the sample size in this study. Therefore, to increase the study's power and consider the possibility of exclusion and dropout, we increased the sample size to 20 patients (10 patients in each group).

t tests - Means: Difference between two independent means (two groups)

Analysis:	A priori: Compute required sample size		
Input:	Tail(s)	=	Two
	Effect size d	=	2.0092394
	α err prob	=	0.05
	Power (1-β err prob)	=	0.8
	Allocation ratio N2/N1	=	1
Output:	Noncentrality parameter δ	=	3.4801047
	Critical t	=	2.2281389
	Df	=	10
	Sample size group 1	=	6
	Sample size group 2	=	6
	Total sample size	=	12

Actual power = 0.87930

5. What were the confounding factors?
According to the reviewer's comments, age, gender, preoperative levels of systolic and diastolic blood pressure, lactate, heart rate, and blood oxygen, underlying diseases of blood pressure and diabetes mellitus were potential confounders in this study. To control for the effects of these confounders, we used a randomized block design to assign patients to treatments (control and DEX). Table 1 and 2 show that randomization adequately controlled for the effects of confounders. There was no statistically significant difference between the DEX and control groups in any of the variables before operation.

6. Did you only include elective patients?
According to the reviewer's comments, patients were randomly assigned to the study based on surgical priority, operating room availability, and patient acceptance, without any intervention in their placement. However, during the analysis, it was found that most patients underwent surgery more than 24 hours after admission, which did not include emergency cardiac surgeries.

7. Primary and secondary outcomes are the same.
According to the reviewer's comments, the primary endpoint was the percentage of patients who showed adverse effects during Dex administration and post-operation. But, the secondary endpoints were the hemodynamic parameters, respiratory characters, arrhythmia incidence and laboratory information.

8. Please revise and correct the references.
According to the reviewer's comments, the references were corrected.

9. English editing is required.
According to the reviewer's comments, the manuscript was edited grammatically and English writing.

10. This study is not suitable for the original article, but it can evaluate as short communication or case series.

The authors thank the reviewer for his/her valuable evaluation.

Kind regards

Reviewer 3:
Dear AE,
This study provides a valuable preliminary insight into the safety and efficacy of Dexmedetomidine in open-heart surgery.. With a few adjustments in design and presentation, this work could form a strong foundation for larger, more definitive trials:

- Some sentences lacks references, for example first sentence of background.
According to the reviewer's comments, the background was revised and highlighted in the manuscript.

-The study reports that recovery times were similar between the groups but does not explore other important postoperative outcomes like pain scores, delirium, or time to extubation.: Dexmedetomidine has been shown to reduce postoperative delirium, improve pain control, and hasten extubation in other studies, but these critical outcomes are not evaluated here. A detailed assessment of postoperative outcomes, including pain, delirium, extubation time, ICU stay duration, and long-term complications, would provide a more comprehensive understanding of Dex's benefits.
According to the reviewer's comments, our manuscript primarily focuses on the collateral effects resulting from the administration of dexmedetomidine during cardiac surgical procedures. It delves into several common concerns that arise in this context, such as bradycardia—a condition characterized by an abnormally slow heart rate—and significant fluctuations in blood pressure that can occur during and after surgery. In addition to these critical cardiovascular implications, the manuscript also takes into account the drug's influence on various other important factors, including the management of pain control in patients, the timing of extubation following surgery, and the overall length of stay in the intensive care unit (ICU) for these patients. By examining these interconnected aspects, the paper aims to provide a comprehensive understanding of how dexmedetomidine affects not only physiological responses but also the broader recovery experience for individuals undergoing cardiac interventions.

-The study mentions some adverse effects (e.g., hypotension, bradycardia, and tachycardia) but does not discuss the severity, duration, or management of these events in detail.: The lack of granularity in adverse event reporting makes it challenging to assess the clinical relevance and safety profile of Dexmedetomidine in this setting. Detailed adverse event data, including the timeline, intervention required, and clinical impact, should be reported for better safety assessment.

In response to the esteemed reviewer's comments, it is important to note that common adverse events in cardiac surgery include hypotension, hypertension, bradycardia, tachycardia, respiratory depression, and hypoxia, as well as postoperative issues like nausea, vomiting, pain, and respiratory depression. Among these, hypotension and arrhythmias related to dexmedetomidine administration are the primary concerns during cardiac surgery. This study focused on the perioperative adverse events detailed in Table 3, and we documented all adverse events, treatments, and patient management according to the pre-designed protocol. In addition, all recorded events were mild, as added in the result section.

Table 3. Adverse effects of Dex during pre-pump on and after pump-off in cardiac surgery.

Character	Hypotension N (%)	Hypertension N (%)	Bradycardia N (%)	Tachycardia N (%)	Hypoxia N (%)	Total N (%)
Control (n=10)	3 (30%)	0	1(10%)	2 (20%)	0	4 (40%)

Dex (n=10)	1 (10%)	0	0	0	0	1 (10%)
p-value	0.582	-	1	0.474	-	0.303

In addition, all of events were mild and this point was added in the result section (Main efficacy measures; page 10). And, lack of some other details were inserted in the limitation section as follows: “another limitation was that we couldn’t include the adverse event timeline, required intervention, and their clinical impact in our study, because of operating room status”.

-The study applies multiple statistical tests but does not address the potential for Type I errors due to repeated testing on a small sample.: Repeated testing increases the likelihood of false-positive results, and the study does not mention any corrections (e.g., Bonferroni adjustment) for multiple comparisons. Use appropriate statistical corrections and ensure the methodology is rigorous, especially for small sample sizes.

According to the reviewer’s comments, In the body of the manuscript, no Bonferroni adjustment was required since the comparisons were not repeated measures. They present the statistical test results comparing two groups at a single time point.

However, according to the reviewer’s comment in the supplementary file, repeated measures were only performed within groups separately using the Friedman test to prevent an increase in type I errors.

-While the study mentions anti-inflammatory effects of Dexmedetomidine, it does not measure inflammatory markers (e.g., C-reactive protein, IL-6): Without these measurements, it is unclear whether Dex’s purported anti-inflammatory benefits contributed to the observed outcomes. Suggestion: Please Include measurements of inflammatory markers to substantiate claims of anti-inflammatory effects.

According to the reviewer’s comments, this manuscript reports on a phased research project. Initially, we assessed feasibility and patient safety; upon confirmation, we proceeded to measure inflammatory cytokines. We aim to present the results following the study's completion and data analysis.

However, it was revised as follows:

“Although our data did not show a significant difference between the groups in lactate level, the change of before pump and after pump was higher in the control group than Dex group. However, the pattern of lactate level in both groups was incremental (hyperlactatemia; without metabolic acidosis), which was statistically significant between the before the pump and after the pump in each group. Moreover, Dex increased lactate level with lower intensity compared to the control, which may mean that Dex increased lactate clearance through its intrinsic effect as a selective α-2-adrenergic agonist and sympatholytic role (32). There is evidence that revealed inflammation, diabetes, surgery, hypoxia and cancer lead to an increase in lactate level (33-35). On the other hand, the previous studies reported that Dex suppressed inflammatory stress responses, sympathetic nervous activation, and hypoxia, which were stimulated by cardiac surgery (5,6,28). Moreover, Dex decreased lactate level through modulation of adrenergic in sheep with septic shock (32). Therefore, Dex may improve circulation in cardiac surgery by reducing lactate level in line with hemodynamic stability which was observed in this study.”

Associate Editor's Comments:

Associate Editor 1:
Dear EIC,
Thanks to the authors and appreciation to the researchers. The manuscript is a valuable research. But some revisions are needed. Authors should revise it based on reviewers comments.

EIC Decision:

Dear Author,
Thank you for submitting the article. It needs some revision. Please revise it based on Reviewers and AE comments.

Uploaded Files by Reviewers/Associate Editor/ or EIC: Below, you can find the list of files attached by reviewers or associate editor or EIC during the review process (if any).

No file

Reviewer Assistant Comments:

These comments were generated by AI based on your manuscript. Please review them and consider incorporating the suggestions to enhance your article.

Based on the provided text of the study titled "Double-blind, randomized, controlled pilot trial to specify collateral effect and safety of perioperative Dexmedetomidine in patients undergoing open heart surgery," I will apply the CONSORT checklist for randomized trials to evaluate the reporting quality of the study.

CONSORT Checklist Evaluation

1. **Title and Abstract**
    - **Title**: The title identifies the study as a randomized trial.
    - **Abstract**: A structured summary is not provided in the text.
2. **Introduction**
    - **Background and Objectives**: The background provides a rationale for the study, discussing coronary artery stenosis and the role of Dexmedetomidine. The objectives are clearly stated.
3. **Methods**
    - **Trial Design**: The study design is described as a double-blind, randomized controlled trial.

- **Participants**: Eligibility criteria are not explicitly detailed in the text.
- **Interventions**: The interventions for both the Dex and control groups are specified.
- **Outcomes**: Primary and secondary outcomes are defined, but details on how they were assessed are lacking.
- **Sample Size**: The sample size is mentioned (20 participants), but the method for determining this size is not provided.
- **Randomization**: The method of randomization is not described.
- **Blinding**: The text indicates that the trial is double-blind, but details on who was blinded are not provided.
- **Statistical Methods**: The statistical methods used to compare groups are not detailed.

4. **Results**
   - **Participant Flow**: There is no flow diagram showing the number of participants at each stage.
   - **Baseline Data**: Characteristics of participants are not provided.
   - **Numbers Analyzed**: The number of participants analyzed in each group is mentioned.
5. **Discussion**
   - **Key Results**: Key results are summarized, but limitations of the study are not discussed.
   - **Generalisability**: The generalizability of the findings is not addressed.
6. **Other Information**
   - **Funding**: There is no mention of funding sources.

Summary of Findings

The study provides some essential information about the trial design, interventions, and outcomes. However, it lacks several critical elements required by the CONSORT guidelines, including a structured abstract, detailed methods for randomization and blinding, statistical analysis methods, participant flow, and discussion of limitations and generalisability.

Recommendations

To improve the reporting quality of this study, the authors should:

- Include a structured abstract summarizing the trial design, methods, results, and conclusions.

  According to recommendation, it was revised.

- Provide detailed eligibility criteria and methods for participant selection.

  According to recommendation, the detail of inclusion and exclusion criteria were provided in the method section.

- Describe the randomization process and blinding methods used.

  According to recommendation, the randomization process and blinding methods were inserted with details.

- Include a flow diagram to illustrate participant flow through the study.

  According to recommendation, it was inserted in the manuscript as figure 1.

- Discuss the limitations of the study and the generalisability of the findings.

  According to recommendation, these sections were added.
  “Limitations
  The present study had the following limitations: the small sample size that might be affected the study power and results. The changes of some variables did not investigate time-dependently, especially during surgery. The patients’ inflammatory mediators, ICU or hospital stay and laboratory markers were not measured. Another limitation was that we couldn’t include the adverse event timeline, required intervention, and their clinical impact in our study, because of operating room status.”

- Report any funding sources.

  There is no funding in this study.

By addressing these points, the study would adhere more closely to the CONSORT guidelines, enhancing its transparency and reproducibility.

2 Revision 1

4 comments · 18 Dec 2024 – 15 Jan 2025

Referee 2 Reviewer — ACCEPT — 18 Dec 2024

Dear AE,
The great effort in improving the manuscript is highly appreciated.
The authors have addressed all the comments.

Referee 1 Reviewer — MINOR REVISION — 30 Dec 2024

Dear Author

Thank you for considering the reviewer comments. I suggest you change some of the old references.

Thank you

Associate Editor — MINOR REVISION — 15 Jan 2025

Dear Editor-in-Chief,

I would like to extend my gratitude to the authors for their contribution and commend the researchers for their valuable work presented in the manuscript. However, I believe that certain revisions are necessary, and I kindly request the authors to consider incorporating these suggested changes based on the provided comments.

Editor-in-Chief — MINOR REVISION — 15 Jan 2025

Dear Author,
Your manuscript still needs some revision. Please revise it based on the reviewers' and AE's comments.

3

Revision 2

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.

Dear reviewers,

Dear reviewers and associate editor, we would like to thank you for taking time out of your busy schedule to review our manuscript and provide your constructive comments. We have provided a point-by-point response to your concerns. Throughout the manuscript's text, all changes are highlighted in yellow. We hope that you find our responses satisfactory.

Reviewers' Comments:

Reviewer 1:
Dear Author
The great effort in improving the manuscript is highly appreciated.
The authors had addressed the all comments.
The authors thank the reviewer for his/her valuable evaluation.

Reviewer 2:
Dear Author
Thank you for considering reviewer comments. I suggest you changes some of old references.
The authors thank the reviewer for his/her valuable evaluation.

According to the reviewer's comments, the old references were changed as follows:

4. Banerjee D, Feng J, Sellke FW. Strategies to attenuate maladaptive inflammatory response associated with cardiopulmonary bypass. Frontiers in Surgery. 2024; 11:1224068.

5. Cai YE, Xu H, Yan J, Zhang L, Lu YI. Molecular targets and mechanism of action of dexmedetomidine in treatment of ischemia/reperfusion injury. Molecular medicine reports. 2014;9(5):1542-50.

7. Nair VA, Gladston DV, Krishna KM J, Koshy RC. Effects of intravenous dexmedetomidine on perioperative haemodynamics and quality of emergence in patients undergoing head and neck surgery following general anaesthesia—a comparative randomized, double-blind placebo-controlled study. Ain-Shams Journal of Anesthesiology. 2022;14(1).

8. Zhou W, Wang J, Yang D, Tian S, Tan C, Yang Y, Sui W, Sun J, Zhang Z. Effects of dexmedetomidine on glucose-related hormones and lactate in non-diabetic patients under general anesthesia: a randomized controlled trial. Minerva Anestesiologica. 2021;88(1-2):8-15.

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3 Revision 2

4 comments · 26 Jan 2025 – 1 Feb 2025

Referee 2 Reviewer — ACCEPT 26 Jan 2025

Thanks for the valuable study and required corrections.

Referee 1 Reviewer — ACCEPT 1 Feb 2025

Dear Author

Thank you for this work.

With the best regard

Associate Editor — ACCEPT 1 Feb 2025

Dear EIC.
Previous errors have been corrected, and there are no further recommendations.

Editor-in-Chief — ACCEPT 1 Feb 2025

Dear authors.
Thanks for your valuable efforts in carefully revising the manuscript.
Your manuscript is acceptable now.