PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of dexmedetomidine infusion during general anaesthesia on incidence of postoperative delirium in elderly patients after major non-cardiac surgery: study protocol of a randomized, double-blinded and placebo-controlled trial
AUTHORS	Wang, Bojie; Li, Chunjing; Hu, Jian; Li, Huaijin; Guo, Chao; Wang, Zhenhan; Zhang, Qiaochu; Mu, Dongliang; Wang, Dong-Xin

VERSION 1 – REVIEW

REVIEWER	Andrea Ortu Cambridge University Hospitals - Addenbrooke's Hospital, Cambridge, UK
REVIEW RETURNED	30-Oct-2017

GENERAL COMMENTS	Just some minor points: - p 9 line 19 - add "criteria" to "inclusion and exclusion" - the treatment in both intervention and control group differs from European practice, particularly regarding the use of nitrous oxide and use of continuous infusion of morphine during the postoperative period. This could limit the external validity of the study. - Not clear to me the way they deal with missing data. Using the last record for all missing data can be misleading particularly if an high number of missing data is registered. - Otherwise is a well designed study and will be interesting to see the results

REVIEWER	Dr Lachlan F. Miles Department of Anaesthesia Austin Health Melbourne, Australia
REVIEW RETURNED	08-Nov-2017

GENERAL COMMENTS	The authors present a single-centre, double blinded, randomised controlled trial, examining the role of dexmedetomidine in the prevention of acute post-operative delirium in elderly patients undergoing major non-cardiac surgery. The study is relatively pragmatic, well-designed, and appears generally feasible. However, there are some points of concern that I feel would benefit from further revision of the manuscript. I have assessed the protocol using the Cochrane risk of bias tool. Random sequence generation – The study is blinded using a system of opaque envelopes containing a random number sequence and a 1:1 allocation ratio. The numbers are created by an independent statistician who is separate from the study team. There is low risk of

	selection bias. Allocation concealment – Allocation is performed by an independent study coordinator who is also responsible for study drug compounding. It is not clear from the protocol whether or not this coordinator has any contact with, or knowledge of patients prior to allocation. This should be clarified in order to ensure that this category is rated “low risk of bias”. At present, a conservative reviewer would rate it as “unclear”. Blinding of participants and personnel – The treating anaesthetist will be given one of two clear, colourless solutions that will be infused at the same rate. On the surface, blinding of participants is therefore ensured. However, because dexmedetomidine has the potential for profound haemodynamic effects, blinding of participants and personnel is not guaranteed, as the patients will be awake when they receive the study drug initially, and the personnel may need to deal with the associated haemodynamic effects. A similar charge was levelled at the POISE trial, and the consequences of beta-blockage. At present, this category is rated “unclear risk of bias”. The authors should provide some additional reference or data concerning the haemodynamic effects of dexmedetomidine at this dose in order to improve this rating. In the event that there are substantial haemodynamic effects, then the blinding of the treating anaesthetist will be limited. In addition, the MAC sparing effect of dexmedetomidine may result in a reduction of the amount of anaesthetic required to maintain BIS, resulting in further risk of inadvertent unblinding of the anaesthetist. Further data on the MAC reducing effects of dexmedetomidine should be included. Detection bias – Outcome assessment will be performed by investigators performing post-operative follow up. These investigators will presumably be separate from those involved in the intra-operative care of patients. The proposed delirium assessment tools (CAM and CAM-ICU) are appropriate, and the training by psychiatrists is also commendable. Some additional information regarding the background of investigators and the duration of the training program will be valuable. CAM has substantial inter-observer variability unless extensive training is undertaken. It should be briefly articulated what this training involves. Attrition bias – This is difficult to assess without some knowledge of the amount of missing data. The unblinding part of the protocol is a little concerning, as it allows unblinding in the event of an SAE. In the event that there is a marked haemodynamic response to dexmedetomidine, then this population could be unblended and excluded from the per protocol analysis. Consequently, there may be fewer frailer patients in the intervention group, and this may confound the results. Investigators may wish to further clarify the precise incidents that they feel will lead to unblinding, and whether the intervention may increase their incidence. Reporting bias – As mentioned above, further information is required regarding the duration and nature of the training program to perform the CAM, and the background of investigators undertaking post-operative follow up. However, this area appears at low risk of bias, provided the investigators can satisfy me that administration of dexmedetomidine will not lead to an excessively high risk of unblinding of patients in the intervention group, particularly those who are frail.

	Overall, the manuscript is reasonably well written, but does appear to be littered with several minor grammatical errors. This is understandable, given the background of the authors. A comprehensive review by a copy editor should solve most of these problems.

REVIEWER	Parli Raghavan Ravi Command Hospital Air Force Bangalore INDIA
REVIEW RETURNED	12-Nov-2017

GENERAL COMMENTS	Queries to authors 1. Please elaborate the risk factors . for example male gender, habits like alcoholism etc 2. Explain briefly how elderly are at risk of developing POD . 3. What are the types of surgeries patient underwent? How many are males ? 4. How many patients received blood transfusion 5. What are the post-operative investigation protocol like serum electrolytes 6. Please justify the selection of Dexmeditomedine in preventing POD with similar studies 7. What was the pre operative sleep patterns of patients 8. Is sleep disorder patients were included / excluded in the studies 9. Please explain how was intraoperative/ post operative hypothermia was managed

VERSION 1 – AUTHOR RESPONSE

Response to editor and reviewers

Editorial Requests:
Q1: We note that there are some discrepancies between the outcome measures reported in your manuscript and those reported in the Chinese Clinical Trial Registry. Please update the registry record accordingly or provide an explanation for these discrepancies.

Response: We are sorry that we did not input all secondary outcomes at the website of Chinese Clinical Trial Registry. We have updated the information of registration.

Q2: Please revise the ‘Strengths and limitations’ section of your manuscript. This section should relate specifically to the methods of your trial.

Response: We revised the ‘Strengths and limitations’ section according to your suggestions.

Reviewer: 1
Reviewer Name: Andrea Ortu
Institution and Country: Cambridge University Hospitals - Addenbrooke's Hospital, Cambridge, UK
Competing Interests: None declared

Just some minor points:

Q1: p 9 line 19 - add "criteria" to "inclusion and exclusion"

Response: We added the word “criteria”.

Q2: the treatment in both intervention and control group differs from European practice, particularly regarding the use of nitrous oxide and use of continuous infusion of morphine during the postoperative period. This could limit the external validity of the study.

Response: Routine practice might be different among different centers. It is true that the single center design limits the external validity of our results. We mentioned this in the part of “Strengths and limitations (page 5, lines 10-12)” and “Discussion (page 17, lines 3-6)”.

Q3: Not clear to me the way they deal with missing data. Using the last record for all missing data can be misleading particularly if an high number of missing data is registered.

Response: In our previous study similar to the present one, the loss-to-follow up rate was less than 6%. In the present study, we stated that “For patients who are discharged or died within 5 days after surgery, the results of last delirium assessment will be considered the results of the missing data (page 12, line 22-25).” This is a frequently used method to deal with the missing data of delirium assessment (Lancet 2016; 388: 1893–902). For secondary endpoints, missing data will not be replaced. The number of patients with missing data will be reported.

Response to Reviewer: 2
Reviewer Name: Dr Lachlan F. Miles
Institution and Country: Department of Anaesthesia Austin Health Melbourne, Australia

The authors present a single-centre, double blinded, randomised controlled trial, examining the role of dexmedetomidine in the prevention of acute post-operative delirium in elderly patients undergoing major non-cardiac surgery. The study is relatively pragmatic, well-designed, and appears generally feasible. However, there are some points of concern that I feel would benefit from further revision of the manuscript. I have assessed the protocol using the Cochrane risk of bias tool.

Q1: Random sequence generation – The study is blinded using a system of opaque envelopes containing a random number sequence and a 1:1 allocation ratio. The numbers are created by an independent statistician who is separate from the study team. There is low risk of selection bias.

Response: Thank you.

Q2: Allocation concealment – Allocation is performed by an independent study coordinator who is also responsible for study drug compounding. It is not clear from the protocol whether or not this coordinator has any contact with, or knowledge of patients prior to allocation. This should be clarified in order to ensure that this category is rated “low risk of bias”. At present, a conservative reviewer would rate it as “unclear”.

Response: We clarified this in the revised manuscript: “A study coordinator, who has no knowledge of patients before randomization and does not participate in anesthesia and postoperative follow-up of enrolled patients, will open envelop for random numbers and prepare study drugs before induction of anesthesia (page 9, lines 18-21).”

Q3: Blinding of participants and personnel – The treating anaesthetist will be given one of two clear, colourless solutions that will be infused at the same rate. On the surface, blinding of participants is therefore ensured. However, because dexmedetomidine has the potential for profound

haemodynamic effects, blinding of participants and personnel is not guaranteed, as the patients will be awake when they receive the study drug initially, and the personnel may need to deal with the associated haemodynamic effects. A similar charge was levelled at the POISE trial, and the consequences of beta-blockage. At present, this category is rated “unclear risk of bias”. The authors should provide some additional reference or data concerning the haemodynamic effects of dexmedetomidine at this dose in order to improve this rating. In the event that there are substantial haemodynamic effects, then the blinding of the treating anaesthetist will be limited. In addition, the MAC sparing effect of dexmedetomidine may result in a reduction of the amount of anaesthetic required to maintain BIS, resulting in further risk of inadvertent unblinding of the anaesthetist. Further data on the MAC reducing effects of dexmedetomidine should be included.

Response: Thank you for your comments. In clinical practice, we do not tell patients that “we are giving study drugs”. For general participants who usually do not have any experiences of receiving dexmedetomidine, they will not realize or try to distinguish that they are receiving dexmedetomidine or placebo. Of course, it is possible that the participant is a professional, such as an anesthesiologist by chance, who will be able to distinguish dexmedetomidine or placebo. However, in our experience, an opportunity like that is very rare.

The hemodynamic effects of dexmedetomidine are dose-dependent. That is why we chose a relative small loading dose (0.6 g/kg administered in 10 minutes). However, clinically obvious hemodynamic changes (especially bradycardia) still occur in some patients even with such a small loading dose. And dexmedetomidine infusion will decrease the consumption of anesthetics during anesthesia maintenance. Therefore, it is not difficult for an experienced and careful anesthesiologist to guess whether the study drug is dexmedetomidine or placebo. In the present study, anesthesiologists who take care of patients (participants) in the operating room take charge of intraoperative data collection; they will not be involved in postoperative follow-up. Postoperative follow-ups are performed by another group of investigators. And anesthesiologists for intraoperative care and investigators for postoperative follow-up are not allowed to exchange patients’ information during the study period. In this way, the blinding of investigators is guaranteed.

In the part of “Method and analysis” of the revised manuscript, we stated: “Investigators who are responsible for postoperative follow-up and delirium assessment are not involved in anesthesia and perioperative care; they are not allowed to exchange patients’ information with anesthesiologists who take care of patients in the operating room (page 12, lines 5-8). In the part of “Discussion”, we discussed this as a limitation of the study: “… because of the hemodynamic and anesthetic-sparing effect of dexmedetomidine, it is not very difficult for the experienced anesthesiologists to guess which study drug is administrated. This might weak the blinding to anesthesiologists. However, in the present study, investigators who are responsible for postoperative follow-up and delirium assessment are not involved in anesthesia and perioperative care; and they are not allowed to exchange patients’ information with anesthesiologists who take care of patients in the operating room. In this way the blinding of investigators to study group assignment can be guaranteed (page 16, lines 15-22).”

In present study, besides oxygen and nitrous oxide at a ratio of 1:1, total intravenous anesthesia is performed for all patients. The consumption of anesthetics (including propofol and sufentanil) will be reported in the final report.

Q4: Detection bias – Outcome assessment will be performed by investigators performing post-operative follow up. These investigators will presumably be separate from those involved in the intra-operative care of patients. The proposed delirium assessment tools (CAM and CAM-ICU) are appropriate, and the training by psychiatrists is also commendable. Some additional information regarding the background of investigators and the duration of the training program will be valuable.

CAM has substantial inter-observer variability unless extensive training is undertaken. It should be briefly articulated what this training involves.

Response: We added the following statement in the revised manuscript: “Investigators who are responsible for postoperative follow-up are not involved in anesthesia and perioperative care, and are not allowed to exchange patients’ information with anesthesiologists who take care of patients in the operating room. Before the beginning of the study, investigators are trained to follow the study protocol and to perform delirium assessment and the training process is repeated at 4 to 6-month intervals during the study period.2-3, 31 The 4-hour training courses of delirium assessment include the following contents: (1) lectures regarding signs/symptoms, diagnosis and treatment of delirium by psychiatrists; (2) training courses of the use of CAM and CAM-ICU on patient-actors (trained ICU physicians or nurses who act as patients with or without delirium) conducted by psychiatrists. The process continued until 100% agreement is achieved in diagnosing delirium (page 12, lines 8-16).”

Q5: Attrition bias – This is difficult to assess without some knowledge of the amount of missing data. The unblinding part of the protocol is a little concerning, as it allows unblinding in the event of an SAE. In the event that there is a marked haemodynamic response to dexmedetomidine, then this population could be unblended and excluded from the per protocol analysis. Consequently, there may be fewer frailer patients in the intervention group, and this may confound the results. Investigators may wish to further clarify the precise incidents that they feel will lead to unblinding, and whether the intervention may increase their incidence.

Response: The dose of dexmedetomidine used in the present study is within the range of routine clinical practice. And, in the present study, frail patients who might not tolerate dexmedetomidine are excluded according to exclusion criteria. These include patients with … (5) severe bradycardia (heart rate less than 40 beats per minute), sick sinus syndrome or atrioventricular block of degree 2 or above; (6) severe hepatic dysfunction (Child-Pugh grade C); or (7) renal failure (requirement of renal replacement therapy) (please see exclusion criteria: page 8, line 24 to page 9, line 3). According to our experience, the numbers of patients who cannot tolerate dexmedetomidine administration will be very rare. However, we defined the criteria of unblinding in order to guarantee patients’ safety, i.e., occurrence of severe adverse events or any unexpected deterioration in the patient’s clinical status. Severe adverse events are defined as severe events which might result in patient’s disability/deformity, prolonged in-hospital stay, or life threatening events.

Q6: Reporting bias – As mentioned above, further information is required regarding the duration and nature of the training program to perform the CAM, and the background of investigators undertaking post-operative follow up. However, this area appears at low risk of bias, provided the investigators can satisfy me that administration of dexmedetomidine will not lead to an excessively high risk of unblinding of patients in the intervention group, particularly those who are frail.

Response: As we stated in the response to Q4 and also in the revised manuscript: “Investigators who are responsible for postoperative follow-up are not involved in anesthesia and perioperative care, and are not allowed to exchange patients’ information with anesthesiologists who take care of patients in the operating room. Before the beginning of the study, investigators are trained to follow the study protocol and to perform delirium assessment and the training process is repeated at 4 to 6-month intervals during the study period.2-3, 31 The 4-hour training courses of delirium assessment include the following contents: (1) lectures regarding signs/symptoms, diagnosis and treatment of delirium by psychiatrists; (2) training courses of the use of CAM and CAM-ICU on patient-actors (trained ICU physicians or nurses who act as patients with or without delirium) conducted by psychiatrists. The process continued until 100% agreement is achieved in diagnosing delirium (page 12, lines 8-16).”

As for the potential risk of unblinding, we exclude frail patients who might not tolerate dexmedetomidine according to exclusion criteria in the present study; and the dose of dexmedetomidine used in the present study is within the range of routine clinical practice. According to our experience, the numbers of patients who cannot tolerate dexmedetomidine administration will be very rare. We will report the number of patients who are unblinded during intervention in our final results. Please also see response to Q5.

Q7: Overall, the manuscript is reasonably well written, but does appear to be littered with several minor grammatical errors. This is understandable, given the background of the authors. A comprehensive review by a copy editor should solve most of these problems.

Response: Thank you for your comments. We rechecked the manuscript and corrected grammatical errors as far as we can.

Response to Reviewer: 3
Reviewer Name: Parli Raghavan Ravi
Institution and Country: Command Hospital Air Force Bangalore, INDIA
Competing Interests: Nil

Q1: Please elaborate the risk factors, for example male gender, habits like alcoholism etc

Response: We will collect these baseline data of enrolled patients according the protocol. These data will be report in final manuscript.

Q2: Explain briefly how elderly are at risk of developing POD.

Response: We stated this in the revised manuscript: “Prevalence of delirium varies from 12% to 51% in patients after non-cardiac surgery, and its prevalence increases with age.2-3 (page 6, lines 5-7)”

Q3: What are the types of surgeries patient underwent? How many are males?

Response: In present study, we will enroll “Elderly (age ≥ 60 years) patients who are scheduled to undergo elective non-cardiac surgery with expected duration ≥ 2 hours under general anesthesia (page 8, lines 19-21);” and we will exclude patients who are scheduled to undergo neurosurgery or surgery for traumatic brain injury (page 8, lines 24-25). As the study is still recruiting patients, we cannot provide the exact data at the moment but will report these results in our final results. According to our previous study, about 68% of patients will undergo intra-abdominal surgery; about 17% of patients will undergo intra-thoracic surgery; the rest will undergo other kinds of surgery. And about 60% of patients will be males (Lancet. 2016 Oct 15; 388(10054): 1893-1902).

Q4: How many patients received blood transfusion.

Response: As the study is still going on, we cannot provide the exact data at the moment. We will report this result in our final results. According to our previous study, about 16% of patients will receive blood transfusion during surgery (Lancet. 2016 Oct 15; 388(10054): 1893-1902).

Q5: What are the post-operative investigation protocol like serum electrolytes

Response: Postoperative managements including laboratory tests (such as serum electrolytes, hemoglobin, etc.) will be performed according to routine clinical practice, except those described in the protocol (such as postoperative patient-controlled analgesia, page 11, line 19 to page 12, line 1).

Investigators will “followed up twice daily during the first 5 postoperative days and then weekly until 30 days after surgery (page 12, lines 4-5)” and collect data (see Outcome assessment, page 12, lines 3 to page 14, line 4).

Q6: Please justify the selection of Dexmeditomedine in preventing POD with similar studies

Response: We discussed this problem in the part of “Introduction” as below: “Use of dexmedetomidine during general anesthesia may reduce POD. In pediatric patients undergoing tonsillectomy and cardiac surgery, intraoperative infusion of dexmedetomidine lowered the incidence of emergence delirium.23,24 In adult patients undergoing cardiac surgery and microvascular free flap surgery, intraoperative dexmedetomidine (comparison with normal saline) slightly decreased the incidence of delirium, although the differences were not statistically significant between two groups possibly due to underpowered sample size.25,26 In a recent study of Deiner et al.,27 use of dexmedetomidine during general anesthesia did not reduce delirium after major non-cardiac surgery in the elderly. However, in that study, anesthesia depth was not monitored and the consumption of anesthetics (such as propofol and fentanyl) was similar between the two groups. It was possible that patients in the dexmedetomidine group received deeper anesthesia which might have increased the risk of delirium.27 Therefore, the effects of dexmedetomidine administered during general anesthesia on the occurrence of POD need to be evaluated further (page 7, lines 8-22).”

Q7: What was the pre operative sleep patterns of patients

Response: In the present study, we do not collect data regarding preoperative sleep patterns. It is true that preoperative sleep disorders might affect the incidence of postoperative delirium as suggested by some authors (Am J Geriatr Psychiatry. 2012 April; 20(4): 317–326; J Clin Sleep Med 2015;11(8):907–913; J Am Geriatr Soc. 2017 Mar 17. doi: 10.1111/jgs.14685). However, we collect data regarding preoperative comorbidity and medical therapy. And strict randomization might balance this factor between groups.

Q8: Is sleep disorder patients were included / excluded in the studies

Response: In the present study, we do not exclude patients with preoperative disorders. Patients with preoperative sleep disorders represent a patient population at high risk of postoperative delirium. We want to include these patients and, therefore, extend the validity of our results.

Q9: Please explain how was intraoperative/ post operative hypothermia was managed

Response: We clarified these in the revised manuscript. In the present study, nasopharyngeal temperature is routinely monitored during anesthesia (page 10, line 10). During surgery, “Body temperature is maintained with air-warming and fluid heating systems. The target of nasopharyngeal temperature maintenance during surgery is from 36.0 to 37C (page 11, lines 14-16).” After surgery, “Other postoperative managements were performed according to routine practice (page 12, line 2)”.

VERSION 2 – REVIEW

REVIEWER	Dr Lachlan F. Miles Department of Anaesthesia, Austin Health, Melbourne, Australia
REVIEW RETURNED	27-Dec-2017

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript again. I note that the authors have responded to all of my questions, and to a large extent, have satisfied my concerns.

	A continued issue that has not been able to resolve to my satisfaction is allocation concealment. This relates to two issues: firstly, the researchers do not intend to tell patients when the study drug is being administered to them in the pre-operative period. My personal practice is to inform the patient when any medication that could potentially affect haemodynamics or consciousness is administered to avoid distress. I would be mildly surprised if the ethics committee of the researcher's own hospital did not hold a similar view. Putting aside these concerns, in order to completely eliminate the risk of inadvertent patient unblinding, deliberately omitting informing the patient should be specified in the study protocol, and in this article. The handling editor may wish to consider if there is an ethical issue with not telling an awake patient that they are about to received a study drug unless they have explicitly consented to this. The authors also essentially admit that there is a high chance the case anaesthetist will be unblended by the MAC sparing and haemodynamic effects of the drug. Unfortunately, there is no way of eliminating this from the study design. However, the authors have taken great pains to separate the case anaesthetist from outcome assessment, and to my mind, there is little more that they can do address this issue. Nevertheless, this is an inherent flaw in the study design. On page 11, line 8, the authors note that they will perform "total intravenous anaesthesia" for all patients. However, later in the article they also state they will be using 50% nitrous oxide. The addition of any volatile anaesthetic including nitrous oxide means that the term "TIVA" is incorrect. However, the term "NIVA" has been used to describe this approach. Please correct. The authors have appropriately addressed concerns around reporting and attrition bias. It would be helpful if they could anticipate the anticipated number of unblinding events due to severe adverse effects from the study drug. Perhaps this information can come from any piloting data for this dosing regimen the authors have previously performed. With respect to grammatical errors, some concerns still exist, even in the areas that have been revised. Again, given the background of the authorship group, this is entirely understandable. Further corrections would need to be made, but these are relatively minor. However, given the prestige of the journal to which this manuscript has been submitted, I would hope that these would be made prior to publication in the event this article was accepted. With the addition of the minor revisions I have outlined above, I would consider this manuscript worthy of acceptance. I would be happy to review a revision of this manuscript if the handling editor deemed it necessary.

REVIEWER	Parli raghavan ravi Command hospital Air Force Bangalore India
REVIEW RETURNED	29-Dec-2017

GENERAL COMMENTS	nothing to add

REVIEWER	Andrea Ortu Cambridge University Hospitals - Cambridge (UK)
REVIEW RETURNED	09-Jan-2018

GENERAL COMMENTS	The protocol is adequate for the clinical question and reviewer's notes have been addressed. Some minor grammatical and spelling error are still present.

VERSION 2 – AUTHOR RESPONSE

Point-to-point response to editor and reviewers

Response to editors
Q1: Along with your revised manuscript, please include a copy of the SPIRIT checklist indicating the page/line numbers of your manuscript where the relevant information can be found (http://www.spirit-statement.org/)
Response: We have uploaded the revised copy of SPITIR checklist.

Q2: Please revise the 'Strengths and limitations' section of your manuscript. This section should relate specifically to the methods of your trial. Point #1 does not relate to the trial methods and should be removed.
Response: We have revised this part and deleted Point#1.

Q3: Please ensure that you improve the quality of language in your manuscript, either with the assistance of an English-speaking colleague or with a professional copyediting agency.
Response: We have asked an English-speaking colleague to revise the manuscript.

Response to reviewer 2:
Reviewer Name: Dr Lachlan F. Miles
Institution and Country: Department of Anaesthesia, Austin Health, Melbourne, Australia

Q1: A continued issue that has not been able to resolve to my satisfaction is allocation concealment. This relates to two issues: firstly, the researchers do not intend to tell patients when the study drug is being administered to them in the pre-operative period. My personal practice is to inform the patient when any medication that could potentially affect haemodynamics or consciousness is administered to avoid distress. I would be mildly surprised if the ethics committee of the researcher's own hospital did not hold a similar view. Putting aside these concerns, in order to completely eliminate the risk of inadvertent patient unblinding, deliberately omitting informing the patient should be specified in the study protocol, and in this article. The handling editor may wish to consider if there is an ethical issue with not telling an awake patient that they are about to received a study drug unless they have explicitly consented to this.
Response: In our previous response to allocation concealment, we stated that "In clinical practice, we do not tell patients that "we are giving study drugs". For general participants who usually do not have any experiences of receiving dexmedetomidine, they will not realize or try to distinguish that they are receiving dexmedetomidine or placebo".
We understand your worry about the ethical problem. We performed the following procedures to protect patient's rights and safety. First, written informed consents were signed at least one day before surgery by all enrolled patients or their surrogate. Before signing the consents, we explained to all potential participants the potential benefits and risks as well as procedures of the trial clearly and

thoroughly. All participants knew that they will receive study drug during anesthesia. Second, pre-anesthesia infusion of dexmedetomidine is a common practice in our center. We seldom tell patients the specific name of anesthetics (such as dexmedetomidine or propofol) that we are giving. But we will tell patients the following in order to relieve their anxiety: “Now I am going to give you some anesthetics. You may fell sleepy or dizzy. It’s normal. Then you will fall asleep. Please do not worry, because we will monitor your vital signs carefully and protect your safety.”

Q2: The authors also essentially admit that there is a high chance the case anaesthetist will be unblended by the MAC sparing and haemodynamic effects of the drug. Unfortunately, there is no way of eliminating this from the study design. However, the authors have taken great pains to separate the case anaesthetist from outcome assessment, and to my mind, there is little more that they can do address this issue. Nevertheless, this is an inherent flaw in the study design.
Response: It’s true that MAC sparing and hemodynamic effects of dexmedetomidine are unavoidable. We have taken efforts to lessen its effect on blindness. But, as you said, this is an inherent flaw in the study design.

Q3. On page 11, line 8, the authors note that they will perform “total intravenous anaesthesia” for all patients. However, later in the article they also state they will be using 50% nitrous oxide. The addition of any volatile anaesthetic including nitrous oxide means that the term “TIVA” is incorrect. However, the term “NIVA” has been used to describe this approach. Please correct.
Response: Thank you for reminding us. We deleted the phrase “total intravenous anaesthesia” and revised the description accordingly (page 11, lines 5-11).

Q4: The authors have appropriately addressed concerns around reporting and attrition bias. It would be helpful if they could anticipate the anticipated number of unblinding events due to severe adverse effects from the study drug. Perhaps this information can come from any piloting data for this dosing regimen the authors have previously performed.
Response: Thank you for your suggestion. We did not consider the number of unblinding because of the following reasons. First, we have excluded high-risk patients (such as those with severe bradycardia, sick sinus syndrome or atrioventricular block of degree 2 or above) during patient recruitment. Second, the dosing regimen we adopted in the present study is being used in our daily practice and in a previous trial of patients undergoing cardiac surgery (PLoS One. 2017 Feb 9; 12(2): e0170757). No severe adverse events occurred in our daily practice and no unblinding occurred in our previous trial. Thirdly, the calculated sample size had been enlarged considering the loss to follow-up rate.

Q5. With respect to grammatical errors, some concerns still exist, even in the areas that have been revised. Again, given the background of the authorship group, this is entirely understandable. Further corrections would need to be made, but these are relatively minor. However, given the prestige of the journal to which this manuscript has been submitted, I would hope that these would be made prior to publication in the event this article was accepted.
Response: Thank you for point out this. We have asked an English-speaking colleague to revise the manuscript.

Response to Reviewer: 3
Reviewer Name: Parli raghavan ravi
Institution and Country: Command hospital Air Force Bangalore, India
Please leave your comments for the authors below
nothing to add
Response: Thank you.

Response to Reviewer: 1

Reviewer Name: Andrea Ortu
Institution and Country: Cambridge University Hospitals - Cambridge (UK)
Please leave your comments for the authors below
The protocol is adequate for the clinical question and reviewer's notes have been addressed. Some minor grammatical and spelling error are still present.
Response: We have asked an English-speaking colleague to revise the manuscript.

VERSION 3 – REVIEW

REVIEWER	Lachlan Miles Austin Health, Australia
REVIEW RETURNED	01-Mar-2018

GENERAL COMMENTS	I thank the authors for the opportunity to review their revised manuscript, as well as their addressing the concerns articulated in my previous reply. The authors have essentially acknowledged that the anaesthesia and MAC-sparing effects of dexmedetomidine will render the study unblinded to the treating anesthesiologist. Whilst this has been specifically mentioned in the revision (page 16, line 15), it may also be worth mentioning in the "strengths and limitations" section of the manuscript on page 3. The manuscript has benefited considerably from revision by the authors' English speaking colleague. Some minor grammatical errors remain, but on the whole, the quality of the manuscript is improved. The handling editor may wish to consider if further rewording of certain sections is required. Overall, this study will make an interesting addition to the literature surrounding delirium management following anaesthesia. I await the results with interest.

VERSION 3 – AUTHOR RESPONSE

Response to editors

Q1: Please include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'. This should provide a brief description of any patient involvement in study design or conduct of the study, as well as any plans to disseminate the results to study participants. If patients and or public were not involved please state this.

Response: We added a paragraph under the sub-heading “Patient and public involvement” according to your suggestion (page 8, lines 18-20).

Response to reviewer 2:

Reviewer Name: Dr Lachlan F. Miles

Institution and Country: Department of Anaesthesia, Austin Health, Melbourne, Australia

Q1: I thank the authors for the opportunity to review their revised manuscript, as well as their addressing the concerns articulated in my previous reply. The authors have essentially acknowledged

that the anaesthesia and MAC-sparing effects of dexmedetomidine will render the study unblinded to the treating anesthesiologist. Whilst this has been specifically mentioned in the revision (page 16, line 15), it may also be worth mentioning in the "strengths and limitations" section of the manuscript on page 3.

Response: We added this in the “strengths and limitations” section (page 5, lines 10-11) and also in the section of Discussion (page 17, lines 6-8) of the revised manuscript.

Q2: The manuscript has benefited considerably from revision by the authors' English speaking colleague. Some minor grammatical errors remain, but on the whole, the quality of the manuscript is improved.

Response: Thanks for your comment. We rechecked the manuscript and corrected grammatical errors.

VERSION 4 – REVIEW

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VERSION 5 – REVIEW

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