The use of dexmedetomidine and intravenous acetaminophen for the prevention of postoperative delirium in cardiac surgery patients over 60 years of age: a pilot study [version 1; referees: 1 approved]

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Abstract

Background: Delirium is associated with many negative health outcomes. Postoperative sedation and opioid administration may contribute to delirium. We hypothesize that the use of dexmedetomidine and intravenous acetaminophen (IVA) may lead to reduced opioid consumption and decreased incidence of postoperative delirium. This pilot study aims to assess feasibility of using dexmedetomidine and IVA in cardiac surgical patients, and obtain effect size estimates for incidence and duration of delirium.

Methods: A total of 12 adult patients >60 years of age undergoing cardiac surgery were recruited for the study after IRB approval and randomized into 4 groups: Propofol only (P), Propofol with IVA (P+A), Dexmedetomidine only (D), Dexmedetomidine with IVA (D+A). Preoperative baseline cognition and postoperative delirium was assessed daily until discharge. The feasibility was assessed by the number of patients who successfully completed the study.

Results: All patients completed the study protocol successfully. The total incidence of delirium in the study population was 42% (5/12): 67% (2/3) in the group P, and 67% (2/3) in the group D, 33% (1/3) in D+A group and 0%(0/3) P+A group. The incidence of delirium was 17% (1/6) in the group receiving IVA compared to 67% (4/6) that did not receive IVA. The mean duration of delirium was 0-1 days. One patient expired after surgery, unrelated to the study protocol. One patient in the D group experienced hypotension with systolic blood pressure <90 mm of Hg.

Conclusions: The feasibility of performing a large-scale project is ascertained by the study. Patients receiving IVA had lower incidence of delirium compared to patients not receiving IVA which suggests that IVA may have a role in reducing the incidence of delirium. A prospective randomized, placebo-controlled trial will be the next step in investigating the role of dexmedetomidine and IVA in reducing the incidence of delirium.
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Author roles: Susheela AT: Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Packiasabapathy S: Validation, Writing – Review & Editing; Gasangwa DV: Resources, Validation, Writing – Review & Editing; Patxot M: Resources, Validation, Writing – Review & Editing; O’Neal J: Conceptualization, Investigation, Methodology, Supervision; Marcantonio E: Conceptualization, Investigation, Methodology, Supervision; Subramaniam B: Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Supervision, Validation, Visualization, Writing – Review & Editing

Competing interests: The authors declare that they have no competing interests of conflicts of interest.

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Introduction
Delirium is defined as a change in mental status, characterized by acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. Delirium increases the risk of mortality, readmissions, and accelerated cognitive decline. Around 158 billion dollars of national healthcare cost is attributable to delirium. The incidence of delirium in cardiac surgery is 11–46%. Delirium is preventable in 30–40% of the cases. Some of the modifiable risk factors for delirium include the choice of analgesic and sedatives.

Currently used sedatives, like midazolam, act via GABA receptors and release deliriogenic mediators. Dexmedetomidine is an alpha 2 adrenergic agonist, with no interaction with GABA receptors.

A recent study by Li et al. in 285 elderly cardiac surgical patients evaluated dexmedetomidine versus propofol and showed no difference in the incidence of delirium. A major limitation of this study is that Confusion Assessment Method (CAM) and CAM-ICU are limited assessments and may miss delirium. There are other tools that could help assess cognitive assessment more efficiently. A meta-analysis suggested that the use of dexmedetomidine for sedation in cardiac surgery patients may reduce the incidence of delirium. The first study in the meta-analysis was a retrospective study by Corbett SM et al. that does not mention how delirium was assessed in individual hospitals. The second study by Shehabi Y et al. was not powered adequately and used CAM-ICU for assessing delirium both in intubated and extubated patients which have reduced sensitivity for delirium in verbal patients and could have underestimated the incidence of delirium. The third study was a small study by Maldonado JR et al. of only 118 patients recruited and only 90 patients finally analyzed, with 28 randomized patients excluded for protocol violations which introduce a significant selection bias. It also showed a 94% reduction in the incidence of delirium and this effect size is almost implausibly large and has not been seen in other studies. The final study by Dasta JF et al. was not designed to identify patients with delirium with any specific tools such as CAM and thus could have gross underestimated delirium incidence.

The use of IV acetaminophen (IVA) has been shown in multiple studies to reduce the amount of opioids consumed by patients undergoing surgeries. IVA has never been studied in the context of cardiac surgery and delirium prevention. So, we hypothesized that the use of dexmedetomidine and acetaminophen would provide adequate analgesia, leading to a decreased opioid consumption and decreased incidence of delirium.

Methods
Purpose
This is a pilot trial which ran from 13th November 2013 to 9th April 2015 to assess the feasibility of using IV dexmedetomidine and acetaminophen in the cardiac surgical intensive care unit. The study also aimed to obtain effect size estimates for primary study outcomes which will help power an ongoing large scale randomized trial (NCT02546765, registered on 13th January 2015).

Study design
This is a single-centered, double-blinded, prospective, randomized controlled pilot trial.

Study population
Patients who are 60 years of age or older who were undergoing coronary artery bypass grafting (CABG), and/or valve surgery were included in the study. Exclusion criteria were preoperative left ventricular ejection fraction < 30%, emergent and percutaneous procedures, aortic surgeries, preexisting cognitive impairment, recent seizures, patients on medications for cognitive decline, serum creatinine > 2 mg%, liver dysfunction, known history of alcohol or drug abuse, and hypersensitivity to any of the study drugs. (Figure 1)

Randomization
Fourteen patients were recruited (the initial 2 patients to help train the investigators in the use of cognitive assessments). The remaining twelve patients were randomized into the following 4 groups, containing 3 patients each (1:1:1:1 allocation). (Table 1)

Each patient was allotted a randomization number based on which the pharmacist assigned the study medications.

Study drug administration
Peri-operative anesthetic management was administered according to standard of care. Intra-operative propofol infusion was administered at the clinician’s discretion for patients in propofol group. In the post-operative period, propofol infusion was titrated to 25–100 µg/kg/min. If the patient was randomized to dexmedetomidine group, propofol infusion was avoided inside the operating room (OR). Dexmedetomidine infusion was given after chest closure at a dose of 0.1–1.0 µg/kg/hr. The medications for sedation were continued in the post-operative period until extubation or for a minimal duration of 6 hours. For patients randomized to IVA group, IVA 1 gram was given every 6 hours for the first 48 hours postoperatively up to a total of eight doses.

Patient assessment
Cognitive assessments were conducted using standard battery used for Minimental (MMSE) and Confusion Assessment Method (CAM).

Outcomes of the study
The primary outcome measured was the proportion of patients who completed the protocol successfully, which reflects the feasibility of the study. The incidence of delirium was measured to obtain effect size estimates for future studies. Secondary outcomes included hypotension, duration of delirium, breakthrough analgesic requirements, ICU days, and length of hospital stay.

Results
The baseline characteristics of the patients were comparable in all groups. The total incidence of delirium was 42% (5/12). The incidence of delirium was 67% (2/3) with propofol and 67% (2/3) with dexmedetomidine. Dexmedetomidine+Acetaminophen group had an incidence of 33% (1/3). The Propofol+Acetaminophen group had no occurrence of delirium. Interestingly, only
17% (1/6) of the subjects who received IVA were diagnosed with delirium compared to 67% (4/6) in the group who did not receive IVA. (Table 2) Also, the incidence of delirium was 33% (2/6) in the propofol groups as compared to 50% (3/6) in the dexmedetomidine groups. The mean duration of delirium ranged from 0 to 1 day. (Table 3) Secondary outcomes were similar between the groups. One patient expired after surgery, unrelated to the study protocol. One patient in the dexmedetomidine group experienced a significant hypotension with systolic blood pressure <90 mm of Hg.

Table 1. Table 1 provides all different groups in the study.

<table>
<thead>
<tr>
<th>Group*</th>
<th>Sedation</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (P)</td>
<td>Propofol</td>
<td>No</td>
</tr>
<tr>
<td>Group 2 (P+A)</td>
<td>Propofol</td>
<td>Yes</td>
</tr>
<tr>
<td>Group 3 (D)</td>
<td>Dexmedetomidine</td>
<td>No</td>
</tr>
<tr>
<td>Group 4 (D+A)</td>
<td>Dexmedetomidine</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*All groups will receive bolus doses of IV opioids (morphine and hydromorphone) as needed for breakthrough pain. I.V. Acetaminophen will be given to group 1 and group 3 every 6 hours for 48 hours, postoperatively.
The use of IV dexmedetomidine and acetaminophen in the cardiac surgical patients was feasible. The study protocol was easily incorporated into patient care. All the enrolled patients completed the study protocol. There were no instances where the implementation of the study protocol was abandoned by the physicians. Sedation provided was useful. Apart from the incidence of hypotension in one patient with dexmedetomidine use, no other adverse events recorded directly related to the intervention.

No other statistical evaluation was done due to the small sample size. The overall incidence of delirium in our trial, at 42%, is close to previous reports. The incidence of delirium in patients receiving IVA was 17% compared to 67% in the other group suggesting that IVA may be beneficial in reducing the incidence of delirium following cardiac surgery. The pilot study led to a larger ongoing trial (NCT02546765).

A major limitation of our study is the small sample size, but this was a feasibility trial to study effect size for the design of future larger studies. Also, there was no blinding for the choice of sedatives used in the patients. The assessors were blinded to acetaminophen administration.

A multi-center randomized, controlled trial will be the next step in investigating the role of dexmedetomidine and IVA in reducing the incidence of delirium.
Data availability
F1000Research: Dataset 1. The datasets used and/or analyzed during the current study. No statistical evaluation was done due to the small sample size, 10.5256/f1000research.12552.d180828

Ethics and consent
This study has been approved by the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center (IRB Protocol #: 2013-P-000149). Informed consent was obtained for all subjects prior to initiation of study procedures. The study was conducted from 13th November 2013 to 9th April 2015.

Competing interests
The authors declare that they have no competing interests of conflicts of interest.

Grant information
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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

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Nicolai Goettel
Department of Anesthesia, University of Basel, Basel, Switzerland

In this single center randomized controlled trial (RCT), Susheela and coworkers investigate the use of dexmedetomidine and intravenous acetaminophen for the prevention of postoperative delirium in elderly patients undergoing cardiac surgery. This pilot study primarily aimed to assess the feasibility of a larger RCT with identical interventions.

As a pilot project, the study is methodically sound. Overall, the manuscript is well-written and pleasant to read. The authors applied CONSORT criteria which is a definite plus.

Postoperative delirium has specific features that may be related to surgery (and anesthesia) and has a probable neuroinflammatory component. I therefore do not agree with your statement that 30-40% of delirium cases could be prevented, at least not in your sample of patients undergoing cardiac surgery. So far, multicomponent interventions to prevent delirium have only been proven efficacious in a general population of elderly hospitalized patients.¹

Please also discuss the opioid-sparing effects of intraoperative dexmedetomidine. Next to the missing interaction with GABA receptors, this might be an additional mechanism for delirium prevention when using dexmedetomidine.

Please discuss the reasons to exclude patients with preexisting cognitive impairment from your study. Preoperative cognitive impairment was found to be one of the most important risk factors for postoperative delirium (odds ratio ranged from 6.3 (95% CI 2.9 to 13.7) up to 11.5 (95% CI 6.1 to 20.1)).² By excluding these patients (also in the follow-up RCT), you likely decrease the number of patients affected by the primary outcome measure (postoperative delirium) in your study. It would be interesting to investigate the effects of dexmedetomidine and intravenous acetaminophen in these high-risk patients.

I find it difficult to blind the intravenous administration of propofol and dexmedetomidine. At best, you may try to conceal the study drug from patient, surgeon, ICU caregivers, and investigators by using opaque syringes and lines. Was study drug administration really double-blind?

Was there any kind of standardization in anesthesiologic management? If yes, state drugs and dosage.

At what frequency did you assess patients for postoperative delirium in the ICU/on the ward? Who assessed the patients?
I wish the investigators of this pilot project the best of luck with the larger ongoing trial!

References

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response (Member of the F1000 Faculty) 10 Nov 2017

Ammu Susheela, Department of Anesthesiology, Beth Israel Deaconess Medical Center, USA

Dear Nicolai Goettel,

We sincerely thank you for the opportunity to address the comments of our manuscript. We have thoroughly reviewed the comments. In this letter, we address, point-by-point, all the recommendations.

We thank you for the review.

Response

In this single-center randomized controlled trial (RCT), Susheela and coworkers investigate the
use of dexmedetomidine and intravenous acetaminophen for the prevention of postoperative delirium in elderly patients undergoing cardiac surgery. This pilot study primarily aimed to assess the feasibility of a larger RCT with identical interventions.

As a pilot project, the study is methodically sound. Overall, the manuscript is well-written and pleasant to read. The authors applied CONSORT criteria which is a definite plus.

Thank you

Postoperative delirium has specific features that may be related to surgery (and anesthesia) and has a probable neuroinflammatory component. I, therefore, do not agree with your statement that 30-40% of delirium cases could be prevented, at least not in your sample of patients undergoing cardiac surgery. So far, multicomponent interventions to prevent delirium have only been proven efficacious in a general population of elderly hospitalized patients.1

Thank you. These estimates are from the pilot study result. The ongoing study will inform us better about the effect size.

Please also discuss the opioid-sparing effects of intraoperative dexmedetomidine. Next, to the missing interaction with GABA receptors, this might be an additional mechanism for delirium prevention when using dexmedetomidine.

Thank you. Agreed. It is possible that dexmedetomidine can reduce the analgesic requirements. The ongoing study will inform us of this effect size as well due to the crossover design.

Please discuss the reasons to exclude patients with preexisting cognitive impairment from your study. Preoperative cognitive impairment was found to be one of the most important risk factors for postoperative delirium (odds ratio ranged from 6.3 (95% CI 2.9 to 13.7) up to 11.5 (95% CI 6.1 to 20.1)).2 By excluding these patients (also in the follow-up RCT), you likely decrease the number of patients affected by the primary outcome measure (postoperative delirium) in your study. It would be interesting to investigate the effects of dexmedetomidine and intravenous acetaminophen in these high-risk patients.

Thank you. As this is the first study of this size, we would like to get a homogenous group examined first and definitely the next step is to do the patients with preexisting cognitive dysfunction.

I find it difficult to blind the intravenous administration of propofol and dexmedetomidine. At best, you may try to conceal the study drug from patient, surgeon, ICU caregivers, and investigators by using opaque syringes and lines. Was study drug administration really double-blind?

Thank you. We only double-blinded the Acetaminophen arms.

Was there any kind of standardization in anesthesiologic management? If yes, state drugs and dosage.

Cardiac surgery is the most protocolized intraoperative setting. Patients were induced
with 500mcg of IV fentanyl, 50-100mg of Propofol, and endotracheal intubation was facilitated with 1mg/kg intravenous rocuronium. Anesthesia was maintained with isoflurane (0.6-1.0 MAC) in 100% oxygen with intermittent fentanyl up to a maximum of additional 500 mcg of fentanyl and intermittent rocuronium. All patients were taken intubated to the ICU.

At what frequency did you assess patients for postoperative delirium in the ICU/on the ward? Who assessed the patients?

Assistants trained from Edward Marcantonio’s lab (with initial half a day training session, witnessing the assessments for a few patients and also calibration with gold standard assessor). Postoperative delirium was assessed by a trained study team member with the help of cognitive assessments such as MMSE, CAM-ICU, and CAM starting from the day after the surgery. If cognitive assessments are negative for 3 consecutive days (i.e days 5, 6 & 7), assessments were completed every other day until the date of discharge.

I wish the investigators of this pilot project the best of luck with the larger ongoing trial!

Thank you

**Competing Interests:** The authors report no competing interests.