



RESEARCH ARTICLE

REVISED 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 2; referees: 3 approved, 1 not approved]

Ammu T. Susheela ¹, Senthil Packiasabapathy ¹, Doris-Vanessa Gasangwa¹, Melissa Patxot¹, Jason O'Neal², Edward Marcantonio³, Balachundhar Subramaniam ¹

¹Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA , 02215-5400, USA

²Department of Anesthesiology, Vanderbilt University Medical Center , 1215 21st Ave. S., Suite 5160 MCE NT , Nashville, Tennessee, 37232, USA

³Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA , 02215-5400, USA

v2 First published: 16 Oct 2017, 6:1842 (doi: [10.12688/f1000research.12552.1](https://doi.org/10.12688/f1000research.12552.1))
Latest published: 21 Dec 2017, 6:1842 (doi: [10.12688/f1000research.12552.2](https://doi.org/10.12688/f1000research.12552.2))

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 estimate the effect size for incidence and duration of delirium.

Methods: A total of 12 adult patients >60 years of age undergoing cardiac surgery were recruited 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 completed the study.

Results: All patients completed the study 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 range of 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 (systolic blood pressure <90 mm of Hg.)

Conclusions: The feasibility of performing a 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.

Open Peer Review

Referee Status:

	Invited Referees			
	1	2	3	4
REVISED				
version 2	report	report	report	report
published 21 Dec 2017				
version 1				
published 16 Oct 2017	report	report		

- Nicolai Goettel** , University of Basel, Switzerland
- Michael S. Avidan**, Washington University School of Medicine, USA
- Yahya Shyehabi**, Monash University, Australia
- George Djaiani**, University Health Network, University of Toronto, Canada

Discuss this article

Keywords

delirium, dexmedetomidine, acetaminophen, cardiac surgery, coronary artery bypass grafting (CABG), propofol, cognitive assessments

Comments (0)

Corresponding author: Ammu T. Susheela (asusheel@bidmc.harvard.edu)

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.

How to cite this article: Susheela AT, Packiasabapathy S, Gasangwa DV *et al.* **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 2; referees: 3 approved, 1 not approved]** *F1000Research* 2017, **6**:1842 (doi: [10.12688/f1000research.12552.2](https://doi.org/10.12688/f1000research.12552.2))

Copyright: © 2017 Susheela AT *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Data associated with the article are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

Grant information: Balachundhar Subramaniam is supported by the National Institutes of Health Research Project Grant GM 098406. *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

First published: 16 Oct 2017, **6**:1842 (doi: [10.12688/f1000research.12552.1](https://doi.org/10.12688/f1000research.12552.1))

REVISED Amendments from Version 1

The following changes, applied to the manuscript, are based on the referees' comments:

- Emphasized that only the feasibility of the project is ascertained. We agree that a larger study is needed to draw a concrete conclusion.
- Reasons for the exclusion criteria were mentioned.

See referee reports

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^{1,2}. Delirium increases the risk of mortality, readmissions, and accelerated cognitive decline^{3–6}. Around 158 billion dollars of national healthcare cost is attributable to delirium⁷. The incidence of delirium in cardiac surgery is 11–46%². Delirium is preventable in 30–40% of the cases². Some of the modifiable risk factors for delirium include the choice of analgesic and sedatives⁸.

Currently used sedatives, like midazolam, act via GABA receptors and release deliriogenic mediators⁹. 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 delirium¹⁰. A major limitation of this study is that CAM-ICU is limited in delirium assessments and may miss the diagnosis. 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 delirium⁹. 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 hospitals¹¹. 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 delirium¹². The third study by Maldonado JR *et al.* of recruited 118 patients and 90 patients were finally analyzed. 28 randomized patients were excluded for protocol violations which introduce a significant selection bias¹³. 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 incidence¹⁴. The use of IV acetaminophen (IVA) has been shown in multiple studies to reduce the amount of opioids consumed by patients

undergoing surgeries^{4,15}. 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 thus decreased incidence of delirium.

Methods

Purpose

This is a pilot trial which ran from November 2013 to November 2014 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

A homogenous set of patients were chosen for this feasibility study. 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. Patients who might not get extubated in a reasonable amount of time (hence the EF, aortic surgery exclusion, etc) were excluded. Since Q6H IV acetaminophen was given, any clinical situation that can potentially set up patients for drug toxicity etc. were avoided. (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. In the dexmedetomidine group, 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.

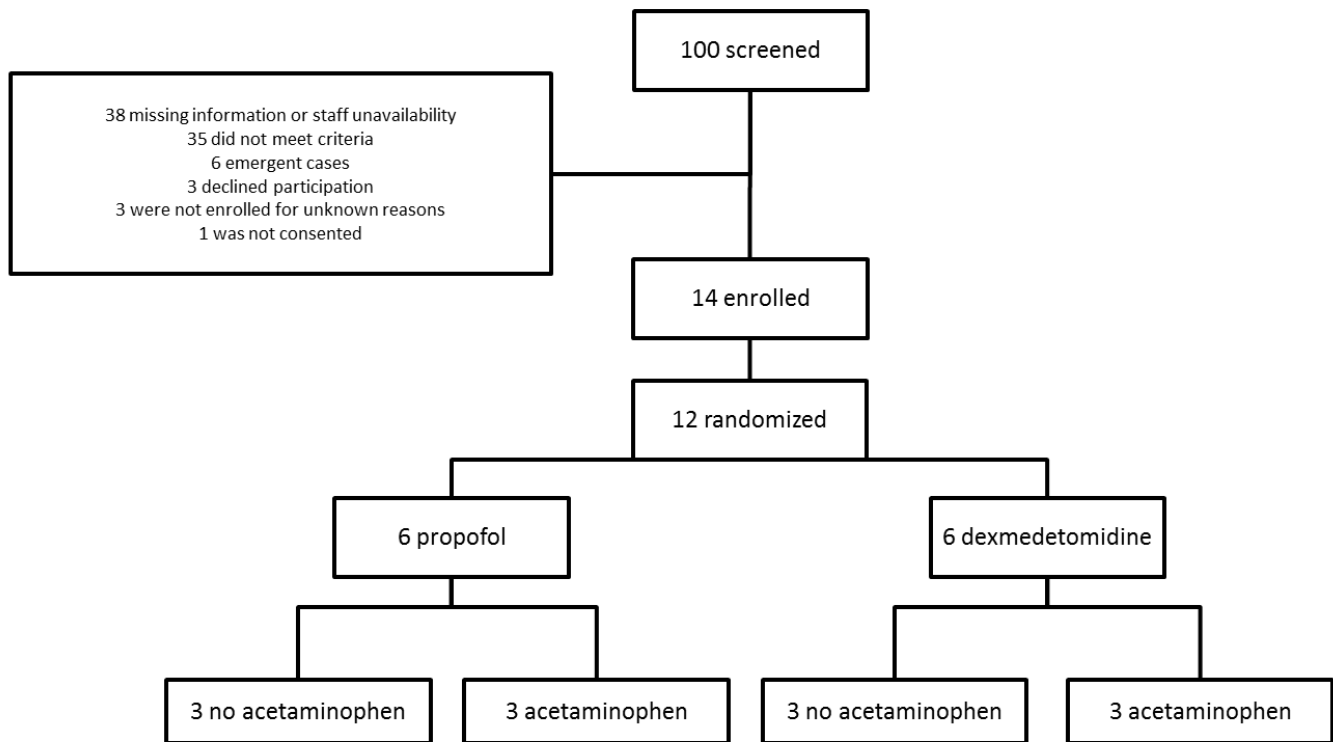


Figure 1. Consort diagram.

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

Group*	Sedation	Acetaminophen
Group 1 (P)	Propofol	No
Group 2 (P+A)	Propofol	Yes
Group 3 (D)	Dexmedetomidine	No
Group 4 (D+A)	Dexmedetomidine	Yes

*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 2 and group 4 every 6 hours for 48 hours, postoperatively.

Patient assessment

Cognitive assessments were conducted using standard battery used for Mini Mental (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

Table 2. Table 2 provides the incidence of delirium and secondary outcomes in the groups receiving propofol, dexmedetomidine, acetaminophen, and no acetaminophen respectively.

	Propofol	Dexmedetomidine	Acetaminophen	No Acetaminophen
Incidence of Delirium % (n/N)	33.3 (2/6)	50 (3/6)	16.7 (1/6)	66.7 (4/6)
Mean Delirium duration [n days]	0.5	1	0.5	1
Opioid consumption mean [SD]*	8.2 [2.02]	11.46 [4.2]	7.54 [2.15]	12.12 [4.06]
Time to extubation (mins) mean [SD]	410.67 [320.25]	439 [239.32]	499.5 [304.63]	350.17 [232.66]
Length of stay (days) mean [SD]	5.67 [0.82]	8.5 [6.5]	7.83 [6.52]	6.33 [1.97]
Adverse events	0	1	0	1
Dexmedetomidine dose mean [SD]**	N/A	0.95 [0.36]	N/A	N/A
Propofol dose mean [SD]***	43.33 [5.16]	N/A	N/A	N/A

*Opioid consumption is expressed in hydromorphone equivalent

**Mean dexmedetomidine dose is expressed as infusion rate of mcg/kg/hr

***Mean propofol dose is expressed as infusion rate of mcg/kg/min

Table 3. Table 3 provides the incidence of delirium and secondary outcomes in the 4 groups in the study namely propofol, propofol + acetaminophen, dexmedetomidine, dexmedetomidine + acetaminophen.

	Propofol	Propofol + Acetaminophen	Dexmedetomidine	Dexmedetomidine + Acetaminophen
Incidence of Delirium % (n/N)	66.6 (2/3)	0 (2/3)	66.6 (2/3)	33.3 (1/3)
Mean Delirium duration [n days]	1	0	1	1
Opioid consumption mean [SD]*	2.84 [1.95]	2.63 [2.2]	5.24 [5.3]	2.4 [2.2]
Time to extubation (mins) mean [SD]	213.67 [42.83]	607.67 [371.66]	486.67 [278.55]	391.33 [242.43]
Length of stay (days) mean [SD]	6 [0]	5.33 [1.15]	6.67 [3.06]	10.33 [9.29]
Adverse events	0	0	0	1

*Opioid consumption is expressed in hydromorphone equivalent

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.

Dataset 1. The datasets used and/or analyzed during the current study. No statistical evaluation was done due to the small sample size

<http://dx.doi.org/10.5256/f1000research.12552.d180828>

Discussion

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 reports². 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](https://doi.org/10.5256/f1000research.12552.d180828)¹⁶

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

Balachundhar Subramaniam is supported by the National Institutes of Health Research Project Grant GM 098406.

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

References

- Bellelli G, Morandi A, Di Santo SG, *et al.*: "Delirium Day": a nationwide point prevalence study of delirium in older hospitalized patients using an easy standardized diagnostic tool. *BMC Med.* 2016; **14**(1): 106. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Inouye SK, Westendorp RG, Saczynski JS: Delirium in elderly people. *Lancet.* 2014; **383**(9920): 911–922. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Inouye SK: Delirium in older persons. *N Engl J Med.* 2006; **354**(11): 1157–1165. [PubMed Abstract](#) | [Publisher Full Text](#)
- O'Neal JB: The utility of intravenous acetaminophen in the perioperative period. *Front Public Health.* 2013; **1**: 25. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Saczynski JS, Marcantonio ER, Quach L, *et al.*: Cognitive trajectories after postoperative delirium. *N Engl J Med.* 2012; **367**(1): 30–39. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Cui V, Tedeschi CM, Kronzer VL, *et al.*: Protocol for an observational study of delirium in the post-anaesthesia care unit (PACU) as a potential predictor of subsequent postoperative delirium. *BMJ Open.* 2017; **7**(7): e016402. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Leslie DL, Marcantonio ER, Zhang Y, *et al.*: One-year health care costs associated with delirium in the elderly population. *Arch Intern Med.* 2008; **168**(1): 27–32. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rudolph JL, Jones RN, Levkoff SE, *et al.*: Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation.* 2009; **119**(2): 229–36. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lin YY, He B, Chen J, *et al.*: Can dexmedetomidine be a safe and efficacious sedative agent in post-cardiac surgery patients? a meta-analysis. *Crit Care.* 2012; **16**(5): R169. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Li X, Yang J, Nie XL, *et al.*: Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. *PLoS One.* 2017; **12**(2): e0170757. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Corbett SM, Rebuck JA, Greene CM, *et al.*: Dexmedetomidine does not improve patient satisfaction when compared with propofol during mechanical ventilation. *Crit Care Med.* 2005; **33**(5): 940–5. [PubMed Abstract](#) | [Publisher Full Text](#)
- Shehabi Y, Grant P, Wolfenden H, *et al.*: Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). *Anesthesiology.* 2009; **111**(5): 1075–84. [PubMed Abstract](#) | [Publisher Full Text](#)
- Maldonado JR, Wysong A, van der Starre PJ, *et al.*: Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics.* 2009; **50**(3): 206–17. [PubMed Abstract](#) | [Publisher Full Text](#)
- Dasta JF, Jacobi J, Sesti AM, *et al.*: Addition of dexmedetomidine to standard sedation regimens after cardiac surgery: an outcomes analysis. *Pharmacotherapy.* 2006; **26**(6): 798–805. [PubMed Abstract](#) | [Publisher Full Text](#)
- Macario A, Royal MA: A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. *Pain Pract.* 2011; **11**(3): 290–296. [PubMed Abstract](#) | [Publisher Full Text](#)
- Susheela AT, Packiasabapathy S, Gasangwa DV, *et al.*: Dataset 1 in: 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. *F1000Research.* 2017. [Data Source](#)

Open Peer Review

Current Referee Status:



Version 2

Referee Report 15 January 2018

doi:10.5256/f1000research.14687.r29300



George Djaiani

Department of Anesthesia and Pain Management, Toronto General Hospital, University Health Network, University of Toronto, Toronto, ON, Canada

The authors report results of a pilot study looking at postoperative administration of acetaminophen in reducing the incidence of postoperative delirium (POD) after cardiac surgery in elderly patients.

I believe that the authors are asking an important question whether adequate or superior pain relief is associated with reduced POD rates after cardiac surgery.

Concerns:

1. It is not clear to me why this pilot study is referred to as a feasibility trial. Both dexmedetomidine and acetaminophen are used routinely in many cardiac centres. Please comment.
2. I would strongly advise against quoting outcome measures as percentages of patients, you have 3 patients per group, e.g., quoting 2/3 (67%) is misleading.
3. The authors found that DEX group received twice as much opioids compared to the other groups. It is in contrary with previous studies identifying opioid sparing effects of DEX. (e.g. Anaesthesiology 2016; 124(2): 362-8; Lancet 2016; 15;388(10054): 1893-1902), however, it could be contributed to small sample size and the DEX administration protocol. Please comment.
4. If I understood correctly DEX was given until extubation or for 6 hours postoperatively. Not a standard administration practice for DEX. Please comment on rational for this design.
5. With respect to pain relief after cardiac surgery, spinal/epidural analgesia has been associated with superior pain relief and significant opioid sparing effects, however, there are no studies that have shown a reduction in delirium rates with either of these techniques. Please comment if acetaminophen may have some intrinsic properties other than analgesia in reducing POD after cardiac surgery.

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?

Partly

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*) 16 Jan 2018

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

Thank you for reviewing the paper. We have thoroughly reviewed the comments. We are addressing below, point-by-point all the suggestions.

Concerns:

It is not clear to me why this pilot study is referred to as a feasibility trial. Both dexmedetomidine and acetaminophen are used routinely in many cardiac centers. Please comment.

Thank you for your comment. The use of IV acetaminophen was more common in our CVICU. Therefore, we chose to see if nurses will be amenable to having this as a placebo-controlled trial.

I would strongly advise against quoting outcome measures as percentages of patients, you have 3 patients per group, e.g., quoting 2/3 (67%) is misleading.

Thank you. Indeed that can mislead. We have also mentioned the number of patients.

The authors found that DEX group received twice as many opioids compared to the other groups. It is in contrary to previous studies identifying opioid-sparing effects of DEX. (e.g. Anaesthesiology 2016; 124(2): 362-8; Lancet 2016; 15;388(10054): 1893-1902), however, it could be contributed to small sample size and the DEX administration protocol. Please comment.

Thank you. Agreed.

If I understood correctly DEX was given until extubation or for 6 hours postoperatively. Not a standard administration practice for DEX. Please comment on the rationale for this design.

Thank you. That is correct. In our hospital, most of the patients get sedation prior to extubation and that was usually around 4-6 hours.

With respect to pain relief after cardiac surgery, spinal/epidural analgesia has been associated with superior pain relief and significant opioid-sparing effects; however, there are no studies that have shown a reduction in delirium rates with either of these techniques. Please comment if acetaminophen may have some intrinsic properties other than analgesia in reducing POD after cardiac surgery.

Thank you. Nonsteroidal anti-inflammatory drugs (NSAIDs) including acetaminophen are the other agents are used in a multimodal regimen for opioid sparing pain management. NSAIDs are generally avoided after cardiac surgery, because of their deleterious effects on the gastric mucosa, kidney and increased risk of bleeding. Intravenous (IV) acetaminophen is a good alternative, with no bleeding risk associated with its use. It inhibits cyclo-oxygenase and consequently the synthesis of pro-inflammatory cytokines.[4] It also decreases the production of inflammatory agents such as histamine and leukotrienes.[5] In addition to its peripheral effects, it may also have effects on the central nervous system which contribute to its analgesic property.[6] Billings et al previously showed that perioperative administration of acetaminophen decreases lipid peroxidation during cardiopulmonary bypass. This study explores the effect of cardiopulmonary bypass and its inflammatory response leading to erythrocyte lysis, and the effect of acetaminophen in its prevention.[7] Although the context is different, the attenuation of lipid peroxidation with secondary inflammation and injury in the immediate postoperative period as seen with acetaminophen may be relevant to its effects on the central nervous system and subsequently on the incidence of delirium. The use of IV acetaminophen has been shown to decrease opioid consumption after surgeries such as hip and knee replacements, cesarean sections, and coronary artery bypass surgeries.

Reference:

1. Djaiani G, Silverton N, Fedorko L, et al. Dexmedetomidine versus Propofol Sedation Reduces Delirium after Cardiac Surgery. *Anesthesiology*. 2016;124(2):362-368.
2. Deiner S, Department of Anesthesiology ISoMaMS, New York, New York, Department of Neurosurgery ISoMaMS, New York, New York, et al. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. *JAMA Surgery*. 2017;152(8).
3. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;388(10054):1893-1902.
4. Graham GG, Scott KF. Mechanism of action of paracetamol. *Am J Ther*. 2005;12(1):46-55.
5. O'Neal JB. The utility of intravenous acetaminophen in the perioperative period. *Frontiers in public health*. 2013;1:25-25.
6. Botting RM. Mechanism of action of acetaminophen: is there a cyclooxygenase 3? *Clin Infect Dis*. 2000;31 Suppl 5:S202-210.
7. Billings FTt, Petracek MR, Roberts LJ, 2nd, Pretorius M. Perioperative intravenous acetaminophen attenuates lipid peroxidation in adults undergoing cardiopulmonary bypass: a randomized clinical trial. *PLoS One*. 2015;10(2):e01

Competing Interests: The authors report no competing interest.

doi:10.5256/f1000research.14687.r29246



Michael S. Avidan

Department of Anesthesiology, Washington University School of Medicine, Saint Louis, MO, USA

The investigators have addressed my concerns.

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) 05 Jan 2018

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

Thank you

Competing Interests: No competing interests to disclose.

Referee Report 28 December 2017

doi:10.5256/f1000research.14687.r29299



Yahya Shyehabi

Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, VIC, Australia

Although this study is considered a pilot trial, the small number of patients 12 divided into 4 groups is a serious flaw in methodology. The interpretation of the data is completely meaningless not even as a feasibility study.

I believe this study should not be more than a run-in phase for a proper pilot with reasonable numbers.

I do not recommend publication in F1000.

Thanks.

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

Partly

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

No

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

No

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

No

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

Partly

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Referee Expertise: Critical care and anaesthesia

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Referee Report 22 December 2017

doi:10.5256/f1000research.14687.r29245



Nicolai Goettel 

Department of Anesthesia, University of Basel, Basel, Switzerland

I do not have further comments to make to this revision of the article regarding the pilot study. I wish the investigators good luck with the follow-up (single- or multicenter) trial.

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) 22 Dec 2017

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

Thank you. We appreciate your comments.

Competing Interests: No competing interests were disclosed

Version 1

Referee Report 27 November 2017

doi:10.5256/f1000research.13591.r27502



Michael S. Avidan

Department of Anesthesiology, Washington University School of Medicine, Saint Louis, MO, USA

This is an interesting and important feasibility study, which seeks to determine whether it is possible to conduct a (large) study evaluating various combinations of sedation/analgesia post cardiac surgery, with the intention of preventing postoperative delirium. In general, with a very small feasibility study, the

investigators demonstrate that conducting such a study might be possible. However this study has important constraints.

1. The investigators state, "The mean duration of delirium was 0-1 days." This appears to be a range.
2. The investigators conclude, "The feasibility of performing a large-scale project is ascertained by the study." I would rather argue that the feasibility of performing a project is ascertained. Whether or not a large-scale project is feasible is not necessarily established.
3. Contrary to the investigators, I do not believe that a 12 patient study with four groups supports the inference "that IVA may have a role in reducing the incidence of delirium." This is over-interpretive of very limited data.
4. I do not agree that using the CAM is a major limitation in delirium research (as the investigators suggest that it might lack sensitivity). I do agree that this might apply to the CAM-ICU.
5. More efficient tools might not necessarily be more sensitive.
6. I am not convinced that a 12 patient pilot trial will produce sufficiently precise estimates to power a large RCT appropriately. Although the absolute difference between proportions (delirium incidence) was 50% (67% minus 17%), the 95% confidence interval for this difference is -13% to 82%. Thus, it is not clear based on this small study what value should be used (estimated difference in delirium incidence between the groups [acetaminophen and placebo]) for the sample size calculation.
7. From the registration site (for NCT02546765), it appears that 120 patients will be included in the (large) trial. This number is likely to be much too small to answer the research question with sufficient precision.
8. The reasons for the exclusion criteria are not clear.
9. With the modified factorial design, was interaction between interventions considered? Specifically, both dexmedetomidine and acetaminophen might have an impact on the outcome of interest (delirium).
10. The (secondary) results of the study were as follows: "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." The investigators should be cautious about over-interpreting these findings, or using these estimates to justify sample size for a large trial. The problem with this would be that 67% is a very high incidence, and is not likely to reflect the incidence with current standard of care (i.e., propofol or dexmedetomidine sedation, without intravenous acetaminophen). Similarly, the incidence of 17% is actually likely to be pretty close to the current delirium incidence in the type of patients who were enrolled to this study (but who receive standard of care).

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?

Not applicable

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

Yes

Are the conclusions drawn adequately supported by the results?

No

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, however I have significant reservations, as outlined above.

Author Response (Member of the F1000 Faculty) 13 Dec 2017

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

Dear Dr. Micheal Avidan,

Thank you for reviewing the paper. We have thoroughly reviewed the comments. We are addressing below, point-by-point all the suggestions.

1. The investigators state, "The mean duration of delirium was 0-1 days." This appears to be a range. **Thank you. Yes. We reported the mean duration as a range.**
2. The investigators conclude, "The feasibility of performing a large-scale project is ascertained by the study." I would rather argue that the feasibility of performing a project is ascertained. Whether or not a large-scale project is feasible is not necessarily established. **Thank you. We agree that only the feasibility of performing a project is ascertained.**
3. Contrary to the investigators, I do not believe that a 12 patient study with four groups supports the inference "that IVA may have a role in reducing the incidence of delirium." This is over-interpretive of very limited data. **Thank you. We agree this is a pre-pilot study indeed. It was a feasibility project and we certainly do not want to overinterpret. Thus, we wrote "IVA may be beneficial in reducing the incidence of delirium following cardiac surgery. " Since this is a feasibility study we agree that a larger study is needed to draw a concrete conclusion.**
4. I do not agree that using the CAM is a major limitation in delirium research (as the investigators suggest that it might lack sensitivity). I do agree that this might apply to the CAM-ICU. **Thank you. Agreed.**
5. More efficient tools might not necessarily be more sensitive. **Thank you. Agreed.**
6. I am not convinced that a 12 patient pilot trial will produce sufficiently precise estimates to power a large RCT appropriately. Although the absolute difference between proportions (delirium incidence) was 50% (67% minus 17%), the 95% confidence interval for this difference is -13% to 82%. Thus, it is not clear based on this small study what value should be used (estimated difference in delirium incidence between the groups [acetaminophen and placebo]) for the sample size calculation. **Thank you. We planned this pilot study as a**

means to assess the feasibility of performing a large-scale project. However, there is no other preexisting data to power the next larger trial. Since this pilot study showed a 66% reduction in the incidence of delirium, for the power calculation, a 50% reduction in the delirium incidence was used. Each group needed 56 patients ($\alpha=0.05$ and $1-\text{Beta}=0.80$).

7. From the registration site (for NCT02546765), it appears that 120 patients will be included in the (large) trial. This number is likely to be much too small to answer the research question with sufficient precision. **Thank you. A multicenter trial is definitely required to answer with precision. However, it will be a major leap to go from a pilot study to a multicenter trial. Thus, we chose to do the second step of testing in a larger sample size with what is known so far. Depending on what this study shows, the obvious next step will be a larger multicenter trial.**
8. The reasons for the exclusion criteria are not clear. **Thank you. We chose a homogenous set of patients to determine the drug efficacy. We wanted to avoid patients who might not get extubated in a reasonable amount of time (hence the EF, aortic surgery exclusion, etc). As we chose to give Q6H IV acetaminophen, we wanted to avoid any clinical situation that can potentially set up patients for drug toxicity etc. Preexisting cognitive dysfunction, etc. could muddle the picture in a 120 patient study. In a larger multicenter trial if and when launched, the heterogeneity can be accounted for and thus need not necessarily be an exclusion criteria.**
9. With the modified factorial design, was interaction between interventions considered? Specifically, both dexmedetomidine and acetaminophen might have an impact on the outcome of interest (delirium). **Thank you. Yes, these interactions will be analyzed in the ongoing trial**
10. The (secondary) results of the study were as follows: "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." The investigators should be cautious about over-interpreting these findings, or using these estimates to justify sample size for a large trial. The problem with this would be that 67% is a very high incidence, and is not likely to reflect the incidence with current standard of care (i.e., propofol or dexmedetomidine sedation, without intravenous acetaminophen). Similarly, the incidence of 17% is actually likely to be pretty close to the current delirium incidence in the type of patients who were enrolled to this study (but who receive standard of care). **Thank you for the caution. We agree with all the comments.**

Competing Interests: The authors report no competing interests.

Referee Report 09 November 2017

doi:10.5256/f1000research.13591.r27423



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

1. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999; 340: 669–76.
2. National Institute for Health and Care Excellence. NCGC National Clinical Guideline Centre. Delirium: diagnosis, prevention and management. <http://www.nice.org.uk/guidance/cg103/evidence/full-guideline-134653069>.

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.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research