

Dexmedetomidine vs morphine and midazolam in the prevention and treatment of delirium after adult cardiac surgery; a randomized, double-blinded clinical trial

ABSTRACT

Background: The aim of this clinical study was to evaluate the efficacy of neurobehavioral, hemodynamics and sedative characteristics of dexmedetomidine compared with morphine and midazolam-based regimen after cardiac surgery at equivalent levels of sedation and analgesia in improving clinically relevant outcomes such as delirium.

Methods: Sixty patients were randomly allocated into one of two equal groups: group A = 30 patients received dexmedetomidine infusion (0.4–0.7 µg/kg/h) and Group B = 30 patients received morphine in a dose of 10–50 µg/kg/h as an analgesic with midazolam in a dose of 0.05 mg/kg up to 0.2 mg/kg as a sedative repeated as needed. Titration of the study medication infusions was conducted to maintain light sedation (Richmond agitation-sedation scale) (–2 to +1). Primary outcome was the prevalence of delirium measured daily through confusion assessment method for intensive care.

Results: Group A was associated with shorter length of mechanical ventilation, significant shorter duration of intensive care unit (ICU) stay ($P = 0.038$), and lower risk of delirium following cardiac surgery compared to Group B. Group A showed statistically significant decrease in heart rate values 4 h after ICU admission ($P = 0.015$) without significant bradycardia. Group A had lower fentanyl consumption following cardiac surgery compared to Group B.

Conclusion: Dexmedetomidine significantly reduced the length of stay in ICU in adult cardiac surgery with no significant reduction in the incidence of postoperative delirium compared to morphine and midazolam.

Key words: Dexmedetomidine; midazolam; morphine; postoperative delirium

Introduction

Postoperative delirium in cardiac surgery patients is as an acute mental disorder presented with fluctuation in cognition with increased morbidity and mortality. During intensive care unit (ICU) stay, complications such as self-extubation exit of life-saving catheters and asynchrony between patient

and ventilator, sternum instability, and the need for surgical revision of the sternal wound may increase.^[1] The wide range in reported incidences of delirium (3%–52%) was explained by the different study designs and different methods of assessing delirium.^[2] There is evidence to support inflammation in the pathogenesis of delirium in both peripheral and central

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tissues with C-reactive protein (CRP) as a marker for infection and inflammation.^[3]

Postcardiac surgery sedation protocols reduce stress response and provide anxiolysis.^[4] The pain, agitation, and delirium guidelines recommend using dexmedetomidine or propofol instead of benzodiazepines therapy in ICU patients developing delirium.^[5] Dexmedetomidine is highly selective and potent central alpha 2-receptor agonist which binds to transmembrane G protein-binding adrenoreceptors and has no activity on the g-aminobutyric acid system.^[6] Dexmedetomidine has opioid-sparing effects by decreasing central nervous system sympathetic outflow. Dexmedetomidine is unique among sedatives used in the ICU because it produces sedation and analgesia without causing respiratory depression.^[7]

The incidence of pain is up to 50% in medical and surgical patients at rest and up to 80% during common care procedures in ICU patients. The continuous use of opioids as analgesics in up to 90% of mechanically ventilated patients may lead to drug and metabolite accumulation.^[8]

This study was designed to compare dexmedetomidine with morphine and midazolam-based regimen after cardiac surgery at equivalent levels of sedation and analgesia to decrease the incidence of postoperative delirium.

Methods

After approval by the institute ethics committee and registration with the ClinicalTrials.gov (NCT03078946), this study was conducted in Ain Shams university hospitals, from March 2013 to April 2015, on 60 patients undergoing elective cardiac surgery under general anesthesia, at least 60 years old, ASA physical status I and II, 70–100 kg body weight, and height 160–180 cm. Written informed consent was obtained from all patients.

Patients were not admitted to the study if any of the following criteria were present: (1) patient's refusal, (2) allergy to any drugs of the study, (3) history of drug or alcohol abuse, (4) history of uncontrolled diabetes or hypertension, (5) history of chronic pain or daily intake of analgesics within 24 h before surgery, and (6) impaired kidney or liver functions.

Patients were randomly allocated into either of the two groups, A and B postoperatively.

Group A (30 patients) received a loading dose of 1 µg/kg dexmedetomidine (Precedex; Hospira, Precedex 200 mcg/2 ml,

Hospira, Inc, Lake Forest, USA) diluted in 100 ml 0.9% saline infused over 10 min immediately postoperative, followed by continuous infusion of 0.2–0.7 µg/kg/h. Group B (30 patients) received morphine in a dose of 10–50 µg/kg/h as an analgesic (Morphine Sulphate ampoule; 10 mg/1 ml, Misr Co. Egypt) with midazolam in a dose of 0.05 mg/kg up to 0.2 mg/kg (Dormicum ampoule containing 15 mg/3 ml, Roche; USA) repeated as needed. Titration of the study medications infusions included interruption (4 h) and reduction aimed to maintain light sedation (Richmond agitation-sedation scale [RASS] –2 to +1) [Table 1].^[9] This study was designed to be a randomized double-blind parallel clinical trial, in which the patients and the investigators were blinded to the given treatment. Randomization was done using computer-generated number table of random numbers in a 1:1 ratio and conducted using sequentially numbered, opaque, and sealed envelope. The study drugs were prepared by the ICU residents not involved in any other part of the study.

Upon arrival at the ICU, a standardized protocol for postoperative care was implemented for all patients. Infusion rates for all sedative protocols were titrated to achieve and maintain light sedation (RASS –2 to +1) before extubation and (RASS 0) after extubation. All patients were extubated when deemed clinically appropriate according to local protocols. Because of their specific pharmacologic properties (i.e., respiratory depression), patients were weaned off propofol or midazolam infusions before extubation, whereas patients receiving dexmedetomidine were extubated while still on the medication and were kept on the maintenance infusion as deemed clinically necessary for a maximum of 24 h.

Initial assessment and stabilization of both patient groups include clinical examination, hemodynamics (invasive blood

Table 1: Richmond agitation-sedation scale

Score	Term description
+4	Overtly combative and violent to staff
+3	Very agitated and removes tube(s) or catheter(s)
+2	Agitated and fights ventilator
+1	Anxious but no aggressive movements
0	Alert and calm
–1	Drowsy but has sustained awakening (eye contact to voice >10 s)
–2	Light sedation and awakens with eye contact to voice (<10 s)
–3	Moderate sedation with eye opening to voice (but no eye contact)
–4	Deep sedation with no response to voice, but movement or eye opening to physical stimulation
–5	Unarousable with no response to voice or physical stimulation

pressure, heart rate [HR], and drains), activated clotting time, electrocardiography, chest X-ray, and arterial blood gases including sodium and potassium. All patients were allowed to take 200 µg fentanyl and 5 mg midazolam immediately on admission. Electrocardiography, chest X-ray, arterial blood gases including sodium and potassium, kidney function, coagulation profile if valve surgery or bleeding occurred, liver function if delirium occurred and CRP quantitative titer were daily performed at 7 a.m.

Delirium was monitored and reassessed up to a maximum of 7 days after surgery and the assessment takes place in two steps: first, the level of consciousness must be assessed using the RASS. If the patient appears to have a RASS score ≥ 3 , then evaluation of delirium using the confusion assessment method for the ICU (CAM-ICU) can be performed. The CAM-ICU includes the assessment of 4 different features: acute change or fluctuating course of mental status, inattention, altered level of consciousness, and disorganized thinking. CAM-ICU is considered positive when features 1 and 2 and either 3 or 4 are present.^[10] The CAM-ICU was performed once daily before midday, independent of additional analgesia or sedation. Abnormal or delirious behavior was recorded every shift by the bedside nurse (nurse:patient ratio 1:1) and reviewed by the research team. The number of delirium days was determined by following delirious patients until 7 days after surgery. Patients were considered delirium free when they were free of delirium for >24 h and alive.

Group A

Dexmedetomidine was diluted in 5% dextrose, given through a separate line and infusion device clearly marked "DO NOT BOLUS." Intensive care staff were familiar with the unique characteristics of dexmedetomidine sedation, particularly the state of "rousable sedation" where patients respond promptly to verbal stimuli or light touch. A loading dose is usually unnecessary and not recommended due to the risk of hypotension. Group A protocol is shown in Figure 1.^[11]

Group B

- 30 patients received morphine in a dose of 10–50 µg/kg/h as an analgesic with midazolam in a dose of 0.05 mg/kg up to 0.2 mg/kg as a sedative repeated as needed
- Additional analgesia in the form of morphine (1–2 mg) or fentanyl (10–20 µg) IV boluses was given to ensure adequate analgesia. However, this was followed by an increase in morphine infusion by 0.10–0.20 µg/kg/h if the desired analgesia target required frequent boluses of additional analgesics aiming to maximize the infusion rate of morphine up to 50 µg/kg/h
- Additional sedation in the form of small increments of midazolam (0.05 mg/kg up to 0.2 mg/kg IV boluses on

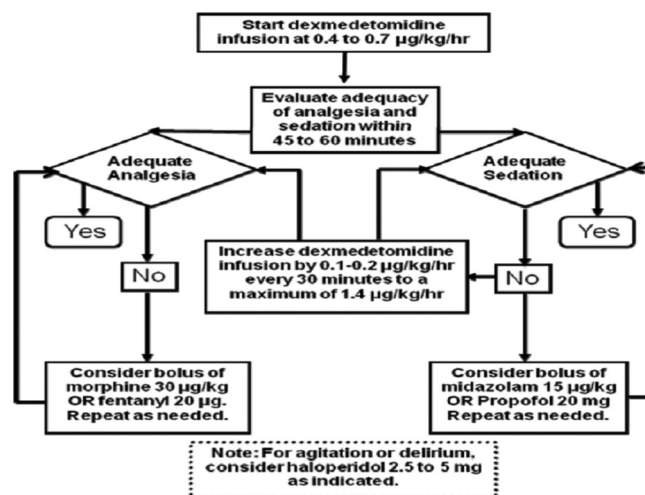


Figure 1: Group A protocol

demand basis) was given to fine-tune targeted sedation. However, this was followed by an addition of propofol infusion (0.5–1 mg/kg/h)

- If delirium and agitation occurred: haloperidol 2.5–5 mg IV repeated boluses.

Titration of the study medication infusion included interruption (4-hourly) and reduction aimed to maintain light sedation (RASS –2 to +1).

Hypotension was considered if there was 20% decrease below the baseline for mean arterial blood pressure, and it was treated with intravenous ephedrine (3–6 mg IV bolus). Bradycardia (HR <55 beats/min) was treated with intravenous atropine (0.6–1 mg).

The following data were collected and compared for each group with respect to:

The primary outcome:

- Incidence of delirium in the study groups
- CRP quantitative titer was measured daily as part of the routine clinical care. The maximum serum CRP level during the ICU stay was designated as max-CRP as a prognostic factor for delirium. Normal concentration of CRP in healthy human serum is between 5 and 10 mg/L, increasing with aging.^[12]

The secondary outcome:

- Difference between morphine and midazolam versus dexmedetomidine in hemodynamic parameters including HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) every 4 h up to 12 h after ICU admission
- Duration of intubation and mechanical ventilation between both groups

- Doses of analgesics and sedatives in both groups
- ICU length of stay in both groups.

Analysis of data

PASS Sample Size Software was used for sample size calculation, where a sample size of 27 patients per group would achieve 80% power to detect a difference of 50% in proportion of delirium in the study groups. The reference group proportion was 0.5. The calculations assumed that two-sided Z-test was used. Thirty patients per group were intended to be included to replace any dropouts.

The collected data were coded, tabulated, and statistically analyzed using IBM Statistical Package for Social Sciences statistics software version 22.0, IBM Corp., Chicago, USA 2013.

Descriptive statistics were done for quantitative as minimum and maximum of the range as well as mean ± standard deviation and for qualitative data as number and percentage.

Inferential analysis was done using 95% confidence interval as well as independent *t*-test in cases of two independent groups with parametric data. In qualitative data, inferential analysis for independent variables was done using Chi-square test for difference between proportions and Fisher’s exact test for variables with small expected numbers. The level of significance at *P* < 0.05 was significant, otherwise nonsignificant.

Results

A total of 78 patients were assessed for eligibility from March 2013 to April 2015 [Figure 2], out of which 70 subjects received study medication after randomization and 60 subjects completed the study (30 patients for each group) and their data were included in the final analysis [Figure 2]. Eight patients were not included in this study on account of patient’s refusal (6 patients) and off-pump coronary artery bypass grafting (two patients). Ten subjects were considered as dropouts after initial randomization and were therefore

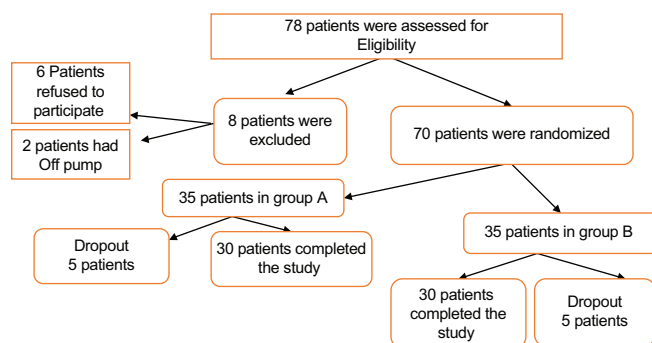


Figure 2: Flowchart of patients

not subjected to further statistical analysis (four subjects needed re-exploration on account of postoperative bleed, three subjects developed cardiogenic shock that necessitate intra-aortic balloon pump, two subjects developed complete heart block after valve surgery, and one subject had a stroke).

Results of the current study did not show any significant difference in the demographic data of the groups of patients regarding age, sex (male to female ratio), body weight, hypertension, diabetes mellitus and operative details [Table 2].

Regarding delirium, maximum CRP, and ventilation time, there were no statistically significant differences between both groups (*P* > 0.05) as shown in Table 3. As regard length of stay, Group (A) showed a significant decrease in length of stay compared to Group (B) postoperatively as shown in Table 3 and Figure 3 (*P* = 0.038).

Group (A) showed statistically significant decreases in HR values 4 h after admission (*P* = 0.015) without significant bradycardia through the whole study. There were no statistically significant changes in HR on admission, 8 or 12 h after admission to the ICU [Figure 4].

Both SBP and DBP readings showed no statistically significant difference between both groups (*P* > 0.05) [Figures 5 and 6].

Regarding doses of analgesics and sedatives in both groups, the required doses of analgesics in both groups showed no significant difference (*P* > 0.05) but in sedative doses showed

Table 2: The demographic data

Variable	Group A <i>n</i> =30	Group B <i>n</i> =30	<i>P</i>
Age (years)			
Mean±SD	65.3±4.8	66.7±5.6	0.303 [^]
Range	60-68	60-71	
Sex			
Females	17 (56.7%)	15 (50.0%)	0.796 [#]
Males	13 (43.3%)	15 (50.0%)	
Weight (kilogram)			
Mean±SD	78.15±12.3	82.7±9.24	0.111 [#]
Range	70-90	73-89	
Hypertension, <i>n</i> (%)	14 (43.3%)	12 (40.0%)	0.602 [#]
Diabetes mellitus, <i>n</i> (%)	13 (40.0%)	15 (50.0%)	0.605 [#]
Operative details			
1-Coronary grafts, <i>n</i> (%)	19 (63.3)	20 (66.7)	<i>P</i> >0.05
2-Valve or valve - coronary graft, <i>n</i> (%)	6 (20.0)	7 (23.3)	<i>P</i> >0.05
3-Redo surgery, <i>n</i> (%)	3 (10.0)	2 (6.7)	<i>P</i> >0.05
4- Other surgery (e.g.Removal of left atrial myxoma), <i>n</i> (%)	2 (6.7)	1 (3.33)	<i>P</i> >0.05

[^]Independent *t*-test, [#]Chi-squared test. *P*<0.05 is statistically significant

tendency toward significance in Group A (a trend toward a lower rate) ($P = 0.084$) [Table 4].

Discussion

The current study suggested that Group (A) was associated with shorter length of mechanical ventilation, significant shorter duration of ICU stay ($P = 0.038$), and with insignificantly reduced incidence of postoperative delirium ($P = 1$) compared to Group (B). Group (A) showed statistically significant

decreases in HR values 4 h after admission ($P = 0.015$) but without significant bradycardia. It had been demonstrated that Group (A) had lower fentanyl consumption following cardiac surgery compared to Group (B).

Results of the current study did not show any significant difference in the demographic data of the groups of patients regarding age, sex (male to female ratio), body weight, hypertension, diabetes mellitus, and operative details.

These results are partially consistent with the findings of Ely et al., who conducted a prospective cohort study on 48 adult patients admitted to the medical ICU of a tertiary care, 24 of whom received mechanical ventilation and all patients were evaluated for the development and persistence of delirium on a daily basis by a geriatric or psychiatric specialist with expertise in delirium assessment using the Diagnostic Statistical Manual IV criteria of the American Psychiatric Association, the reference standard for delirium ratings and they found that most of patients developed delirium in the ICU, and delirium was the most important independent factor for length of stay in the hospital.^[13]

These results are partially in agreement with the findings of Maldonado and Dhimi who found that patients ($N = 225$ patients) admitted to the ICU underwent a rational approach to the identification and treatment of delirium resulted in an accurate and prompt diagnosis, as well as shorter hospital stays, lower incidence of complications during hospitalization, a reduction in the use of restraints, faster recovery, and a substantially greater resolution of confusion by the time of discharge home.^[14]

Table 3: Delirium, Maximum CRP, Ventilation time and Length of stay

Variable	Group A (n=30)	Group B (n=30)	P
Duration of intubation and mechanical Ventilation time (Hours)	4.66±11.72	12.9±16.3	0.075
LOS (days)	2.73±1.66*	4.23±3.5	0.038
Max.CRP during ICU stay (quantitative tire) (mg/L)	127.1±253.29	101±253.3	0.99
Delirium (Patients)	1	2	1

Data were presented as mean±SD. $P < 0.05$ is statistically significant, *Denotes significant difference

Table 4: Doses of analgesics and sedatives

Variable	Group A (n=30)	Group B (n=30)	P
Total morphine (mg)		105.64±106.67	
Total dexmedetomidine (µg/kg/h)	0.724±0.41		
Fentanyl (µg)	176.05±4.73	194.2±2.03	0.216
Midazolam (mg)	6.65±3.1	10.2±7.5	0.084

Data were presented as mean±SD. $P < 0.05$ is statistically significant. SD: Standard deviation

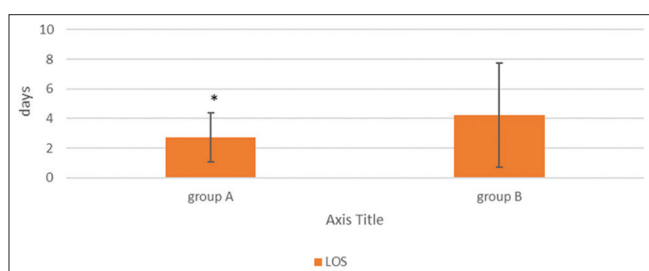


Figure 3: Length of stay in intensive care unit (days). *Denotes significant difference. Lines are mean length of stay and error bars are standard deviation

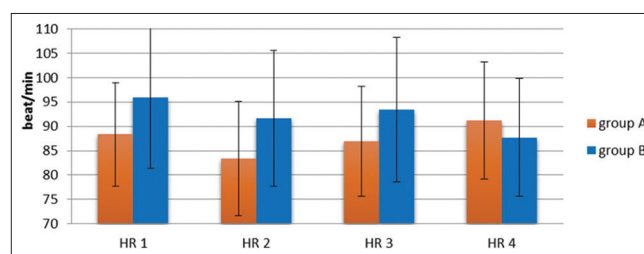


Figure 4: Changes in heart rate (beat/min). HR 1: On admission, HR2: After 4 h, HR3: After 8 h, HR 4: After 12 h. *Denotes significant difference

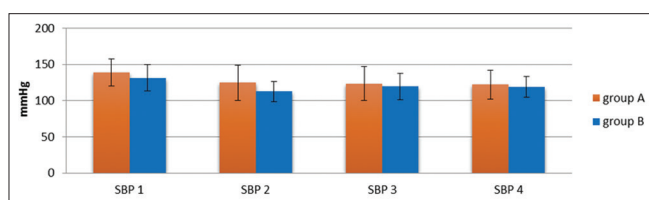


Figure 5: Changes in systolic blood pressure (mmHg). SBP1: On admission. SBP2: After 4 h. SBP3: After 8 h. SBP 4: After 12 h

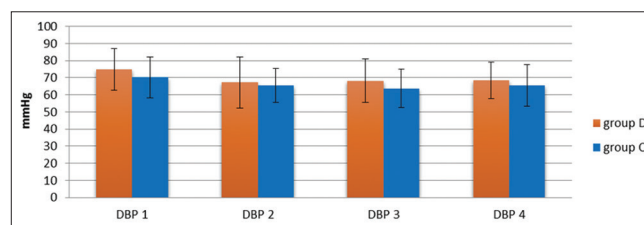


Figure 6: Changes in diastolic blood pressure (mmHg). DBP1: On admission. DBP2: After 4 h. DBP3: After 8 h. DBP 4: After 12 h

Our results were also partially supported with the study of Lundström *et al.*, who demonstrated that using successful intervention programs including all aspects of good medical and nursing care in patients with femoral neck fractures ($N = 199$ patients) resulted in fewer days with delirium, fewer other complications, and shorter hospital stays.^[15]

Partially in agreement with our results, Maldonado concluded that postoperative delirium has been associated with increased morbidity and mortality, increased cost of care, increased hospital-acquired complications, poor functional and cognitive recovery, decreased quality of life, prolonged hospital stays, and increased placement in specialized intermediate and long-term care facilities.^[16] Furthermore, partially in agreement with these results, Maldonado *et al.* who compared dexmedetomidine versus propofol and midazolam on the development of delirium in 90 patients undergoing elective cardiac-valve procedures found that dexmedetomidine was associated with significantly lower rates of postoperative delirium, shorter hospital stays, and better cognitive functioning.^[17]

On the contrary to these results, a study by Lin *et al.* compared dexmedetomidine with a placebo or an alternative sedative agent in an elective cardiac surgery and found that dexmedetomidine significantly reduces the incidence of delirium following cardiac surgery and there was no significant difference in the duration of ICU stay and hospital days following cardiac surgery.^[4]

However, Lin *et al.* had some limitations in their meta-analysis. First, possible heterogeneity of study design, drugs, dosing regimens, and the postoperative recovery unit model precluded meta-analysis of these study results. Second, difficulty maintaining consistency across studies is apparent when different goals for ideal sedation were adopted; for example, some studies required Ramsay level ≥ 3 , while others used levels 2–4, 2 or 3, or 5. Third, inability to compare cost in these trials because drug-related cost was not well-defined provided that dexmedetomidine is currently much more expensive than commonly used drugs (for example, propofol). Finally, there was lack of long-term follow-up in patients treated with dexmedetomidine in the selected articles.^[4]

Also, on the contrary with these results, Shehabi *et al.* compared the prevalence of delirium with dexmedetomidine versus morphine-based sedation in patients undergoing cardiac surgery. The frequency of delirium was assessed daily for the first 5 days after surgery using the CAM-ICU and with a significantly shorter duration of delirium in the dexmedetomidine group.^[18]

This study did not support the anti-inflammatory theory of dexmedetomidine over morphine and midazolam that compared by measurement of maximum CRP as it was statistically insignificant.

On the contrary with this study, Kang *et al.* documented the effects of dexmedetomidine on inflammatory responses in patients undergoing laparoscopic cholecystectomy and found that dexmedetomidine administration during surgery reduced intraoperative and postoperative secretion of cytokines, as well as postoperative leukocyte count and CRP level.^[19]

This study found a tendency toward significance in shorter duration of intubation and mechanical ventilation time (hours) in dexmedetomidine group. Group (A) showed statistically significant decreases in HR values 4 h after admission without significant bradycardia as we didn't use loading dose of dexmedetomidine. There were no significant differences in the total amount of analgesia and a trend towards lower doses of sedatives.

Partially consistent with this study, Chorney *et al.* conducted a retrospective analysis of 99 patients (52 receiving no sedation and 47 receiving dexmedetomidine) admitted to a cardiothoracic ICU after cardiac surgery and found no statistically significant difference in time to extubation between groups, and also, they found that the safety profile did not differ significantly for patients who did or did not receive dexmedetomidine. The incidence of bradycardia in the control group was 3.8% while dexmedetomidine patients had an incidence of 2.1% and hypotension did not occur in any patients in either cohort. In addition, they found that there was no significant difference between control and dexmedetomidine patients with respect to opioid analgesic use.^[20]

A study by Lin *et al.*, partially consistent with these results, found that dexmedetomidine treatment did not appear to reduce morphine equivalents compared with other sedatives and dexmedetomidine was found to significantly increase the risk of bradycardia, but not hypotension. However, on the contrary with this study, Lin *et al.* demonstrated that dexmedetomidine significantly reduced the length of mechanical ventilation.^[4]

Partially consistent with this study, Abd Aziz *et al.* conducted a study on a total of 28 patients who underwent cardiac surgeries randomly assigned to receive either dexmedetomidine or morphine and they found that dexmedetomidine group showed more benefits in sedation and pain levels and extubation time. No significant differences between the two

groups for the outcome measures, except HR, which was significantly lower in the dexmedetomidine group.^[21]

Meanwhile, Barletta *et al.* conducted a retrospective, cohort study of 100 patients to determine the impact of dexmedetomidine on analgesic requirements after coronary artery bypass graft surgery or valvular surgery and found that the dexmedetomidine resulted in reducing opioid needs in patients after cardiac surgery versus those receiving propofol, but this did not reduce durations of mechanical ventilation, using a fast-track cardiovascular recovery unit model.^[22]

Partially consistent with these results, a study by Eremenko *et al.*, performed on 55 cardiovascular surgery patients to compare the efficacy of dexmedetomidine and propofol for short-term controlled sedation and analgesia in the early postoperative period after cardiac surgery and concluded that dexmedetomidine induced less sedation level and more often provided retrograde amnesia with the same duration of mechanical ventilation and awakening rate compared to propofol. Dexmedetomidine provided its own analgesic effect and shortened the length of patient's stay in ICU. Bradycardia was noted more frequently in dexmedetomidine group while arterial hypotension, general malaise and delirium were noted more frequently in propofol group.^[23-25]

On the contrary to this study, Maldonado *et al.* found that dexmedetomidine had opioid-sparing effects due to a significant reduction in fentanyl and total morphine-equivalents compared to midazolam in the postoperative period and partially consistent with this study as no significant difference in fentanyl and total morphine-equivalents was seen between dexmedetomidine and propofol patients.^[17]

Our study presented several limitations. First, the small size of this study raised the possibility that these results were confounded by unobserved imbalance in the baseline characteristics of the two groups. The second limitation was that this single-center design was a potential limitation of the trial with a possible bias by institutional standards of care. The third limitation was that our trial lacked power to show a significant reduction in mortality. Even though the reduction in morbidity in small surgical population gave a remarkable value for this relatively simple intervention, it will need further evaluation in a larger multi-center study. The fourth limitation was that time to hospital discharge, an important outcome due to its economic implications and affected by the presence of postoperative pain should be taken in consideration in further randomized clinical trials.

Conclusion

Using dexmedetomidine versus morphine and midazolam for analgesia and sedation in adult cardiac surgery significantly reduced the length of stay in ICU and significantly did not cause significant bradycardia or hypotension in dexmedetomidine group with no significant reduction in the incidence of postoperative delirium, CRP, duration of intubation and mechanical ventilation, and the amount used of analgesics and sedatives in both groups.

The research team suggested that these results of this work justified the conduct of a larger size, double-blinded randomized controlled trial including patient's aged 60 years or more, determining other inflammatory markers (interleukin [IL]-6, IL-10, tumor necrosis factor alpha and CD64), using of high-sensitivity immunosorbent assay for evaluation of CRP and allowing use of dexmedetomidine up to 1.5 μ /kg/h >24 h, incorporating cost-effectiveness and quality of life analyses.

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Conflicts of interest

There are no conflicts of interest.

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