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Prevalence of Delirium with Dexmedetomidine Compared with Morphine Based Therapy after Cardiac Surgery

A Randomized Controlled Trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study)

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Background: **Commonly used sedatives/analgesics can increase the risk of postoperative complications, including delirium. This double-blinded study assessed the neurobehavioral, hemodynamic, and sedative characteristics of dexmedetomidine compared with morphine-based regimen after cardiac surgery at equivalent levels of sedation and analgesia.**

Methods: **A total of 306 patients at least 60 yr old were randomized to receive dexmedetomidine (0.1–0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$) or morphine (10-70 $\mu g \cdot kg^{-1} \cdot h^{-1}$) with open-label propofol titrated to a target Motor Activity Assessment Scale of 2–4. Primary outcome was the prevalence of delirium measured daily *via* Confusion Assessment Method for intensive care. Secondary outcomes included ventilation time, additional sedation/analgesia, and hemodynamic and adverse effects.**

Results: **Of all sedation assessments, 75.2% of dexmedetomidine and 79.6% ($P = 0.516$) of morphine treatment were in the target range. Delirium incidence was comparable between dexmedetomidine 13 (8.6%) and morphine 22 (15.0%) (relative risk 0.571, 95% confidence interval [CI] 0.256–1.099, $P = 0.088$), however, dexmedetomidine-managed patients spent 3 fewer days (2 [1–7] *versus* 5 [2–12]) in delirium (95% CI 1.09–6.67, $P = 0.0317$). The incidence of delirium was significantly less in a small subgroup requiring intraaortic balloon pump and treated with dexmedetomidine (3 of 20 [15%] *versus* 9 of 25 [36%]) (relative risk 0.416, 95% CI 0.152–0.637, $P = 0.001$). Dexmedetomidine-treated patients were more likely to be extubated earlier (relative risk 1.27, 95% CI 1.01–1.60, $P = 0.040$, log-rank $P = 0.036$), experienced less systolic hypotension (23% *versus* 38.1%, $P = 0.006$), required less norepinephrine ($P < 0.001$), but had more bradycardia (16.45% *versus* 6.12%, $P = 0.006$) than morphine treatment.**

Conclusion: **Dexmedetomidine reduced the duration but not the incidence of delirium after cardiac surgery with effective analgesia/sedation, less hypotension, less vasopressor requirement, and more bradycardia *versus* morphine regimen.**

ANALGESIA and sedation is an important component of the postoperative management of cardiac surgery patients. However, no single agent or combination of agents have shown a clear superiority in improving clinically relevant outcomes such as delirium.[1–3]

Delirium is a very common complication in older people admitted to hospital.[4,5] Given its high incidence, the consequences of delirium place a substantial burden on both patients and healthcare systems as a result of increased morbidity, decline in long-term cognitive function, and higher mortality rates.[6–7]

Although the prevalence of delirium after cardiac surgery can vary from 20–50%,[8–11] predictors of delirium include advanced age, established cognitive impairment, underlying primary cerebral disease, anesthesia, prolonged bypass time, and postoperative sedative use.[12–15] Currently, more than 67% of patients presenting for cardiac surgery are older than 65 yr with increased comorbidities. Furthermore, the surgery performed is more complex, including more valve and redo operations than documented before 2000.[16,17] Given that these patients are at a higher risk of postoperative complications, careful consideration should be given to the choice of postoperative analgesics and sedatives.[18]

A recent systematic review stressed the importance of pain management in reducing the risk of postoperative delirium and cognitive decline. It also demonstrated the paucity of clinical trials addressing these issues, particularly after cardiac surgery.[8] Although there is a strong association between inadequate pain control and risk of postoperative delirium,[9] the drugs used to alleviate pain, particularly some opioids, are known to promote both delirium and postoperative cognitive loss.[10] This paradox highlights the critical balance between adequate pain control, analgesic choice, and delirium reduction.

Dexmedetomidine is a highly selective and potent α_2 adrenergic receptor agonist.[19,20] It provides sedation

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with modest analgesic and possible antidelirium effects with minimal respiratory depression.[21,22] In addition, the use of $\alpha_2$agonists has been associated with lower cardiovascular complications in high-risk noncardiac surgery.[23] Taken together, dexmedetomidine could provide specific advantages over commonly used analgesic and sedative agents after cardiac surgery.

The aim of this randomized, double-blind trial was to assess the effect of an α_2 agonist-based therapy, dexmedetomidine, compared to a morphine-based regimen at equivalent levels of analgesia and sedation, on the prevalence of delirium, ventilation time, hemodynamic profile, and the adequacy of analgesia/sedation in patients older than 60 yr after cardiac surgery.

Materials and Methods

Study Design and Population

This was a randomized, double-blinded, controlled clinical trial. It was conducted in two tertiary referral university-affiliated hospitals between August 2004 and December 2007. The study protocol was approved by the South Eastern Sydney Area Health Service Ethics Committee. Written informed consent was obtained before surgery. Patients were randomized *via* random computer-generated blocks of ten by the clinical trials pharmacist who also prepared study drug solution. All caregivers, including surgeons, anesthetists, and intensive care medical and nursing staff were blinded to the treatment given.

Patients included in the study were 60 yr of age or older and undergoing pump cardiac surgery, including coronary artery bypass grafts (CABG), valve surgery, combination CABG, and/or valve replacement procedures. Patients were excluded from participating in the study if they were allergic to any of the study medications, were receiving other α_2 agonists such as clonidine or psychoactive agents other than night time hypnotics. Patients were also excluded if their preoperative heart rate was less than 55 beats/min and/or systolic blood pressure less than 90 mmHg, if they had a body weight greater than 150 kg or a preoperative creatinine greater than 140 μM (1.6 mg/dl) or a creatinine clearance of less than 50 ml/min (calculated by the Cockcroft Gault formula). In addition, patients with documented preoperative dementia, Parkinson disease, recent seizures and those unable to understand English and thus unable to participate in the delirium assessment were also excluded.

Study Protocol and Drug Infusions

The study drugs were prepared at a concentration of 0.1 $\mu g \cdot kg^{-1} \cdot ml^{-1}$ for dexmedetomidine and 10 $\mu g \cdot kg^{-1} \cdot ml^{-1}$ for morphine. When body temperature was at least 35°C (heated air mattress Bair Hugger® [Augustine Medical, Inc., Eden Prairie, MN] was used to achieve and maintain body temperature between 36 and 37°C) and within 1 h of admission to the cardiothoracic intensive care unit (ICU), the study drug infusion commenced at 3 ml/h without a loading dose. Patients received an infusion of either dexmedetomidine (0.1–0.7 $\mu g \cdot kg^{-1} \cdot ml^{-1}$) or morphine (10–70 $\mu g \cdot kg^{-1} \cdot ml^{-1}$), which was titrated per prespecified protocol to maintain target sedation and adequate analgesia. A propofol infusion and/or boluses were also given if deemed necessary by the medical team for rapid control of a hypertensive episode (systolic blood pressure $>$ 160 mmHg) or unplanned awakening.

Although morphine was chosen as a comparator to maintain blinding of treatment arms, subsequent propofol was added to maintain equivalent sedation. Similarly, open label morphine was allowed in the dexmedetomidine group to achieve equivalent analgesia. The conventional care in our institution uses morphine and propofol, and caregivers are skilled at titrating these two drugs to a target sedation and pain scale.

The ICU staff were familiar with and commonly use the Motor Activity Assessment Scale (MAAS)[24]; it was therefore chosen to mimic normal practice. When patients began to regain consciousness, study drug infusion rates were adjusted to maintain a MAAS score of 2–4. For patients with a MAAS score of 0–1, the study drug infusion was decreased or interrupted as necessary until the target MAAS score was achieved. For patients with a MAAS score greater than 4, the study infusion was increased by 1 ml/h, and additional propofol boluses (25 mg every 5 min as required) followed by an infusion (30–100 mg/h) were used if necessary. Similarly, a graded evaluation of pain control was performed by the bedside nurse (certified in postoperative cardiac care) with MAAS assessments and on need basis. Inadequate pain relief was managed by increasing the study drug infusion by 1 ml/h and an additional open label bolus of 1–2 mg IV morphine. This process was repeated every 15 min until adequate analgesia and target MAAS was achieved.

The study drug infusion was continued until the removal of chest drains, when patient was ready to discharge from ICU, or for up to 48 h of mechanical ventilation, after which sedation was provided per clinician's choice. Furthermore, the study drug infusion could be stopped in patients who were too drowsy but ready to be extubated. After extubation, paracetamol and oral opioids were permitted as required.

Perioperative Management

Patients were premedicated with 1.5–2 mg of oral lorazepam, 7.5–10 mg of intramuscular morphine, and 1.25 mg of droperidol. Anesthesia was maintained with 0.1–0.15 mg/kg midazolam, 15–25 μg/kg fentanyl, 0.2 mg/kg pancuronium and 2–3% sevoflurane in oxygen.

All patients were monitored with routine cardiac surgery hemodynamic monitoring, including a transesophageal echocardiography and a pulmonary artery catheter at the discretion of the anesthetist. In addition, end tidal carbon dioxide and arterial pulse oximetry were continuously monitored. Depth of anesthesia was monitored with bispectral index (BIS) and temperature *via* a nasopharyngeal probe. Cold blood cardioplegia was used, and standard nonpulsatile cardiopulmonary bypass primed with 500 ml of 4% albumin and 1,500 ml of standard crystalloid. Mean arterial pressure on cardiopulmonary bypass was maintained between 50 and 70 mmHg with a blood flow of $2.4\ l \cdot min^{-1} \cdot m^{-2}$.

After surgery, patients were transferred intubated and ventilated to a cardiothoracic ICU under the management of an intensivist-led team. Active warming was performed when required to achieve and maintain tympanic temperature 36.0 to 37.0°C. After achieving adequate intravascular volume, norepinephrine was used to maintain a mean arterial blood pressure of at least 70 mmHg and dobutamine to maintain a cardiac index of at least $2.5\ l \cdot min^{-1} \cdot m^{-2}$. A glyceryltrinitrate infusion was used for blood pressure control. Blood products, including packed red blood cells, were given to maintain a hemoglobin level of at least 8.0 g/dl. When cardiac index was maintained on low-dose inotropes, intraaortic balloon pump (IABP) was rate weaned to a ratio of 1:3 over a 4-h period and was then removed by medical staff. On initial return from theater, patients were ventilated with a tidal volume of 7–8 ml/kg and a positive end expiratory pressure of 7 cm H_2O, respiratory rate of 10 breaths per minute, and Fio_2 of 0.6. Ventilation was weaned per ICU protocol. When patients were spontaneously breathing, the mandatory rate was reduced, and pressure support of 7 cm H_2O above positive end expiratory pressure ventilation was established. Patients were extubated when MAAS was in the target range and when a spontaneous tidal volume of 5–6 ml/kg with a respiratory rate of less than 25 breaths per minute was achieved.

Outcome Measures

The primary outcome of the study was the percentage of patients who developed delirium within 5 days after surgery as determined by the validated Confusion Assessment Method for Intensive Care (CAM-ICU).[25,26] 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. CAM-ICU was not performed in patients who had a MAAS score of 1 or less (coma). Other *a priori* defined delirium-related outcomes included percentage of patients with IABP or valve surgery who developed delirium. The number of delirium days was determined by following delirious patients until 12 days after surgery. Delirium on day 0 (day of surgery) was assessed by using the CAM-ICU for patients who were able to communicate. Patients were considered delirium-free when they were free of delirium for more than 24 h and alive.

Secondary outcomes included the percentage of patients who maintained a MAAS score within the target range (2–4), time to successful extubation (no reintubation within 48 h), length of ICU stay, length of hospital stay, number of patients intubated for greater than 12 h and hospital mortality rate. Additional outcomes included doses of vasopressors, inotropes, vasodilators, and all additional sedatives and analgesics, including aggregate doses of propofol, morphine, and haloperidol.

Adverse Events

Clinical adverse events were monitored in all patients during the ICU stay unless otherwise stated. Adverse events were defined as follows: hypotension as a systolic blood pressure less than 90 mmHg; bradycardia as a heart rate less than 55 beats/min, a new arrhythmia, need for pacing, a troponin rise of at least 3 ng/ml measured daily, premature cessation of study drug, hyperglycemia (blood sugar level $>$ 10 mmol/l), and postoperative nausea and vomiting (requirement for more than three doses of antiemetics). The following were also monitored to hospital discharge: kidney injury (a rise in creatinine of 100% above preoperative value), a new neurologic impairment (other than confusion or delirium) lasting more than 24 h, reintubation, readmission to ICU, postoperative blood transfusion, any culture-positive postoperative infection, return to operating theater, and cardiac arrest of any cause.

Statistical Analysis

After review of published literature at the time of study design, we assumed a 28% incidence of delirium in the control group. The recruitment of 302 patients was needed to detect a clinically relevant 50% reduction in the delirium event rate ($\alpha = 0.05$ and 80% power) with a 1:1 randomization for the entire sample.

As surgery was a critical entry point to the study protocol, data were assessed by using a modified intention-to-treat (ITT) population with primary analysis performed on patients who underwent on-pump cardiac surgery and received a study drug infusion (fig. 1). Continuous data were described by using mean (SD) or median (interquartile range), and categorical data were described by using frequencies and proportions. We used relative risk (RR) and Fisher exact test to compare categorical variables between the two study groups and Mann–Whitney U test to compare continuous variables. However, we used unpaired *t* test assuming unequal variance to compare the mean of the total dose of norepinephrine, dobutamine, and additional morphine and propofol required. Time-to-event analyses were used to compare the effects of the two sedation regimens on resolution to delirium-free (see definition above), extu-

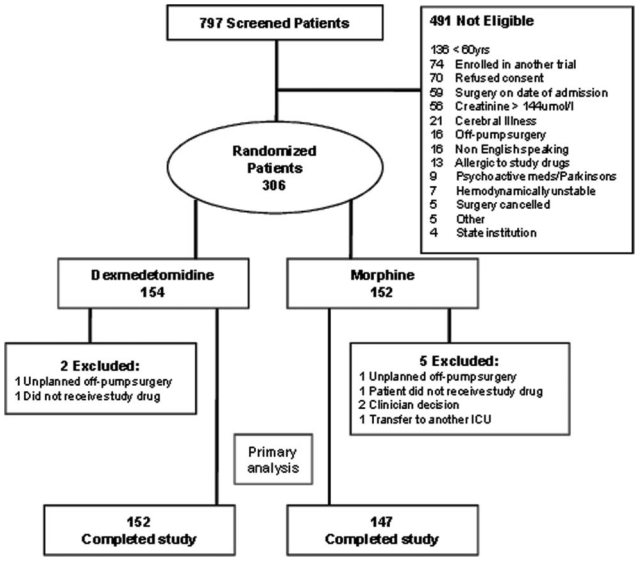

Fig. 1. Patients enrollment flow diagram. This illustrates the flow of all patients screened, excluded, and randomized. Primary analysis conducted on patients who had surgery and received any study drug infusion. ICU = Intensive care unit.

bation, ICU, and hospital lengths of stay. Kaplan-Meier survival curves were used for graphical presentation of these time-to-event analyses (time to extubation and ICU length of stay). Log-rank test as well as hazard ratio from Cox regression model were used to assess the effects of the two sedation regimens. For the resolution to delirium-free analyses, multiple and delayed entries were allowed over the 12 days after surgery. Patients were censored at the time of last observed delirium or at 12 days from the enrollment, whichever occurred first. For the extubation analysis, patients were censored at the time of last observed intubation or at 144 h from enrollment, whichever was first. Censoring for ICU or hospital discharge analyses occurred at time of death or time of discharge from ICU or hospital. To predict which patients were more likely to need prolonged ventilation, a multivariate Cox regression model with forced entry method was performed to identify the clinically relevant variables at baseline. The predictors in the multivariate model, chosen from the literature review and the expert opinions included age, gender, chronic pulmonary disease status (yes/no), types of surgery (valve, combined valve, and CABG *vs.* CABG only), ejection fraction (less than 50%) and elective *versus* nonelective surgery indicator. We considered a two-sided P value of 0.05 or less as indicative of statistical significance. All analyses were completed by using Stata 9.2, 2007 (StataCorp, College Station, Texas, TX).

Results

Enrollment

Figure 1 depicts the enrollment flow diagram. A total of 797 patients were screened, and a total of 299 patients (n = 152 dexmedetomidine, n = 147 morphine regimen) were included in the primary analysis.

Baseline Characteristics

Baseline characteristics and demographics of patients in the two study arms were comparable (table 1). Overall, 84.6% of patients were older than 65 yr. The majority of patients (58.1%) underwent urgent surgery, 29.1% had valve or combined valve/CABG surgery, and 15% required an IABP. Preoperative β-blockers, angiotensin-converting enzyme and angiotensin II inhibitors, diuretics, and statins were continued, and antithrombotic therapy was managed per clinical necessity. The details of comorbidities and operative details are shown in table 1.

Study Drug Administration

The duration of study drug infusion was similar in the two treatment arms with a median dexmedetomidine dose of 0.49 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 49 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of morphine. Both treatment arms achieved comparable target MAAS[24] score, including immediate postanesthesia assessments and after first 6 h as shown in table 2. Most study drug infusions were ceased per protocol; however, seven patients (4.6%) in the dexmedetomidine group and nine patients (6.1%) in the morphine group had their infusions ceased prematurely. In 8 of the 16 cases, this was a result of hemodynamic instability, with five patients in the dexmedetomidine and three in the morphine group. Other reasons included return to theater (three in the morphine and one in the dexmedetomidine), postoperative cardiogenic shock (only one in the morphine group), and clinician decision.

Clinical Outcomes

Incidence of Delirium. The overall incidence of delirium within 5 days was 11.7% (35 of 299), with 8.6% occurring in the dexmedetomidine and 15% in the morphine group (RR 0.571, 95% CI 0.256–1.099, $P = 0.088$; table 2). The duration of delirium was significantly less in dexmedetomidine compared with morphine-treated patients (2 *vs.* 5 days, 95% CI 1.09–6.67, log rank $P = 0.0317$; table 2).

The overall incidence of delirium in a subgroup of patients who required an IABP was 26.7% (12 of 45), with significantly less delirium in patients who were treated with dexmedetomidine (RR 0.416, 95% CI 0.152–0.637, $P = 0.001$; table 2). Numbers were too small to assess the difference in the duration of delirium; nevertheless, the median (interquartile range) delirium days in the dexmedetomidine was 8 (2–9) *versus* 12 (4–12) in the morphine group.

Patients who underwent valvular or combined valve/CABG experienced similar incidence of delirium (RR 1.06, 95% CI 0.263–4.27, $P = 0.923$; table 2).

Table 1. Patient Demographic and Baseline Characteristics

Characteristics*	Dexmedetomidine (n = 152)	Morphine (n = 147)
Age, yrs	71.5 (66 to 76)	71.0 (65 to 75)
Male, n (%)	114 (75.0)	111 (75.5)
BMI, kg/m^2	27.3 (24.7 to 29.4)	27.7 (25.2 to 31.2)
Diabetes, n (%)	45/149 (30.2)	42/146 (28.7)
Hypertension, n (%)	124/149 (83.2)	127/146 (87.0)
History of smoking, n (%)	92/141 (65.3)	100/143 (69.9)
Preop creatinine, mmol/l	90 (80 to 110)	90 (80 to 110)
Preop hemoglobin, g/dl	137 (120 to 148)	138 (123 to 149)
Preop platelets, 10^3/dl	209 (173 to 256)	204 (167 to 243)
Chronic obstructive pulmonary disease		
Moderate, n (%)	25 (16.4)	17 (11.4)
Severe, n (%)	7 (4.6)	6 (4.0)
Left ventricular function		
% Ejection fraction/echo assessment		
<35% or severe impairment, n (%)	7/141 (5.0)	13/138 (9.4)
35 to 49% or moderate impairment, n (%)	22/141 (15.6)	18/138 (13.0)
>50% or normal, n (%)	112/141 (79.4)	107/138 (77.5)
Preop myocardial infarction, n (%)	56/149 (37.6)	53/146 (36.3)
NYHA class III – IV, n (%)	17/141 (12.0)	12/138 (8.7)
Operative details		
Elective surgery, n (%)	58/149 (38.9)	65/146 (44.5)
Urgent, n (%)	91/149 (61.1)	81/146 (55.5)
Coronary grafts, n (%)	90 (59.2)	93 (63.3)
Valve or valve + coronary graft, n (%)	45 (29.6)	47 (32.0)
Redo surgery including valves, n (%)	15 (9.9)	7 (4.8)
Other surgery	2 (1.3)	0 (0.00)
Time on bypass, min	98 (80 to 128)	100 (77 to 120)
Cross clamp time, min	66 (48 to 90)	67.5 (50 to 89)
Intra-aortic balloon pump, n (%)	20/152 (13.2)	25/147 (17.0)

* Continuous variables presented as median (interquartile range) unless otherwise stated. None showed any statistical significance.

BMI = body mass index; NYHA = New York Heart Association classification.

An unplanned *post hoc* analysis excluding patients with IABP showed a comparable incidence of delirium in the dexmedetomidine group (7.6% [10 of 132] *versus* 10.7% [13 of 122]) in the morphine treatment group (RR 0.76, $P = 0.446$ with a median duration of 1 [1–3] *vs.* 2 [1–6], respectively, $P = 0.272$). On day 0, 56 patients could not be assessed (residual anesthesia) for delirium, and 243 patients were assessed with 1 (0.9%) dexmedetomidine- and 5 (3.8%) morphine-treated patients scoring a positive CAM-ICU. Most patients (33 of 35) who developed delirium were diagnosed within 3 days after surgery, with no new delirious patients recorded after day 4 after surgery.

Table 2. Clinical Outcomes and Variables

Outcome Variables*	Dexmedetomidine (n = 152)	Morphine (n = 147)	*P* Value
Delirium outcomes			
Patients with delirium, n (%)	13 (8.6)	22 (15.0)	0.088
Delirium days, median (IQR)	2 [1-7]	5 [2-12]	0.031†
Patients with IABP and delirium, n (%)	3/20 (15)	9/25 (36)	0.001
Patients with valve/combined, n (%)	6/48 (12.5)	6/51 (11.8)	0.923
Study drug dose, $\mu g \cdot kg^{-1} \cdot h^{-1}$	0.48 (0.23–0.76)	49 (20–81)	NA
Time on study drug, h	18 (15–20)	17 (15–20)	0.225
MAAS within target range, n (%)			
Including all assessments ‡	1134/1507 (75.2)	1247/1567 (79.6)	0.516
6 hours after surgery	1315 (87.3)	1418 (90.5)	
Time to extubation, h	14 (10–18.5)	15 (10–22)	0.036§
ICU length of stay, h	45 (24–71)	45 (24–75)	0.148‖
Intraaortic balloon pump, h	40 (26.5–49.5)	48 (26–72)	0.648
Hospital LOS, d	8 (7–11)	8 (7–11)	0.501#
Hospital mortality, n (%)	2/152 (1.32)	4/147 (2.72)	0.442

* Data presented as median (interquartile range) unless otherwise stated; † *P* value from log-rank test; ‡ Including immediate post anesthesia time; §‖# *P* value from log-rank test.

IABP = Intraaortic aortic balloon pump; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; MAAS = motor assessment agitation scale.

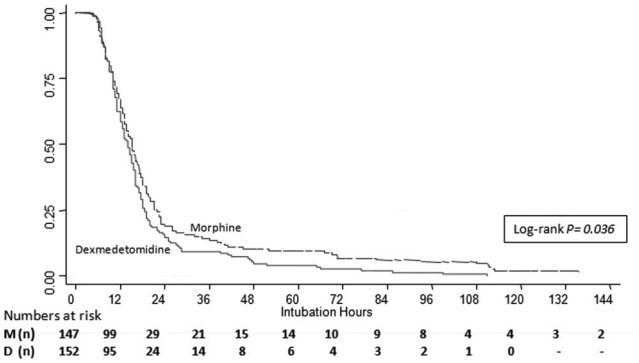

Fig. 2. Kaplan-Meier survival analysis for time to successful extubation. Patients treated with dexmedetomidine were more likely to be extubated earlier, Cox regression model (Hazard ratio 1.27, 95% CI 1.01–1.60, $P = 0.040$). Separation of Kaplan-Meier curves occurred after 18 h. For patients intubated for longer than 12 h (Hazard ratio 1.35, 95% CI 1.00–1.82, $P = 0.047$). D = dexmedetomidine; M = morphine.

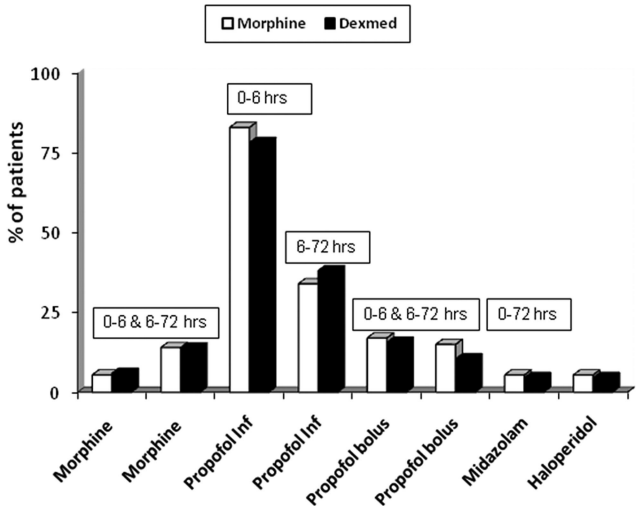

Fig. 3. Patients requiring additional sedation and analgesia. Number and percent of patients receiving open label additional morphine, propofol infusion, or propofol boluses divided into two time frames: 0 to 6 h and 6 to 72 h after surgery. The midazolam and haloperidol histograms are for the total time 0 to 72 h. Dexmed = dexmedetomidine; Inf = infusion.

Intubation Time and ICU Stay. Dexmedetomidine-treated patients were more likely to be extubated earlier than those treated with morphine-based regimen (Hazard ratio 1.27, 95% CI 1.01–1.60, $P = 0.04$ with log-rank test $P = 0.036$; fig. 2). Whereas 37.5% of dexmedetomidine-treated patients *versus* 32.6% in the morphine group were extubated within 12 h, separation between the two groups started to occur after 12 h (fig. 2), with clear separation in patients needing ventilation for more than 18 h. The ICU and hospital length of stay were comparable in both groups (table 2).

Multivariable analysis for predictors of prolonged intubation showed that IABP ($P < 0.001$) or a valve or a combined valve/CABG operation ($P = 0.002$) were significant predictors of prolonged ventilation after surgery. Age, sex, emergency surgery, chronic pulmonary disease, or abnormal LV function did not predict lengthy postoperative ventilation.

Additional Sedation and Analgesia. As a result of the nature of the surgery and residual anesthesia, we assessed the requirements for additional open-label sedatives and analgesics over two time frames: up to 6 h and from 6 to 72 h after surgery. The overall number of patients and (mean ± SD) hourly dose requirements for open label additional morphine were small and comparable in both groups, with dexmedetomidine delivering adequate pain control in 87% of patients (figs. 3 and 4A).

The number of patients requiring an infusion of propofol in the first 6 h was similar in both treatment groups (dexmedetomidine 78.3% *vs.* morphine 83%). After 6 h, propofol requirements substantially dropped in both groups: 38.1% in the dexmedetomidine *vs.* 34% in the morphine group. The (mean ± SD) total dose of propofol infusion needed was significantly lower in the dexmedetomidine-treated group (30.3 ± 4.7 *versus* 35.3 ± 5.2 mg/h in the morphine group; $P < 0.001$). However, the overall requirements for additional propofol boluses mean ± SD was comparable in the dexmedetomidine (33.8 ± 10.5 *versus* 43.6 ± 10.7 mg in the morphine group; $P = 0.084$; figs. 3 and 4, B and C). Similarly, the overall mean requirement for additional morphine was also comparable (0.36 *vs.* 0.34 mg, $P = 0.476$). The number of patients receiving midazolam (mostly commenced in the operating room and in patients with IABP) was less in the dexmedetomidine group (4.6% *vs.* 6.8%), but the aggregate (mean ± SD) dose of midazolam given was significantly higher compared to the morphine group (54.3 ± 14.7 *vs.* 24.8 ± 25 mg; $P = 0.014$), respectively. The subgroup of patients with IABP showed comparable requirements for additional midazolam: 4 of 20 (20%) *versus* 5 of 25 (20%) with an hourly (mean ± SD) dose of 2.60 ± 1.92 mg *versus* 1.58 ± 1.36 mg in the dexmedetomidine and morphine groups, $P = 0.267$. The number of patients receiving haloperidol during the study period was comparable in both groups (4.6% *vs.* 5.4%), with similar (mean ± SD) dose (7.6 ± 4.7 *vs.* 8.6 ± 6.7 mg) in the dexmedetomidine and morphine groups, respectively.

Vasopressor, Inotropic, Vasodilator Therapy, and IABP Requirements. This was assessed hourly for all patients. Drug infusions that were predominantly used included norepinephrine, dobutamine, and glyceryltrinitrate. On admission to the ICU, the number of patients receiving norepinephrine (3.3% *vs.* 4.8%), dobutamine (12.5% *vs.* 15.6%), and glyceryltrinitrate (48% *vs.* 49.7%) were comparable in the dexmedetomidine and morphine groups, respectively. By 12 h, this increased to a peak for norepinephrine (23.7% *vs.* 30.6%, $P = 0.181$), dobutamine (48.7 *vs.* 38.1%, $P = 0.151$), and glyceryltrinitrate (peaked at 8 h) (68.4% *vs.* 68.7%, $P = 0.958$) in the dexmedetomidine and morphine groups, respec-

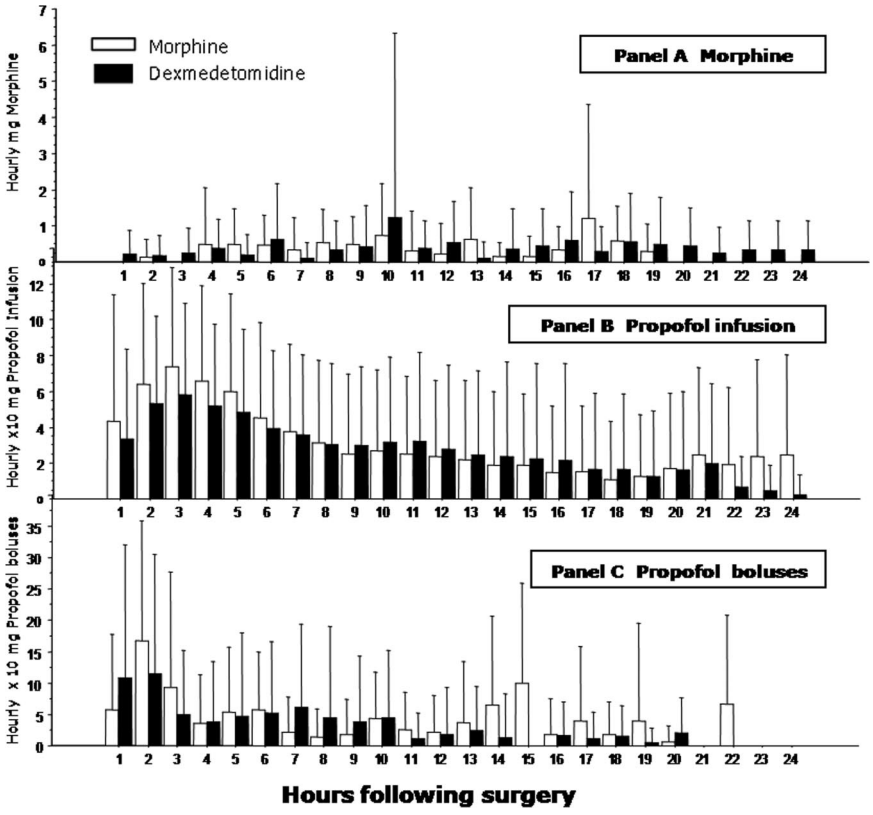

Fig. 4. Aggregate additional open label sedation and analgesia. Hourly (mean ± SD) mg of additional morphine (*A*) and propofol (*B and C*). By using unpaired *t* test, the mean ± SD of total dose of propofol given by infusion was significantly less in the dexmedetomidine group ($P < 0.001$). The mean ± SD of total mg of propofol boluses and additional morphine were comparable ($P = 0.084$ and $P = 0.476$, respectively).

tively. The (mean ± SD) total hourly dose of norepinephrine needed in the first 24 h was significantly less in the dexmedetomidine group: 0.026 ± 0.05 *versus* 0.040 ± 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.001$; fig. 5A). The requirements for dobutamine were comparable in the dexmedetomidine group (3.27 ± 2.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and the morphine group (3.12 ± 3.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $P = 0.178$; fig. 5B) or for nitrate between the two treatments over 24 h after surgery. The number of patients receiving other vasoactive agents was small: epinephrine (3 *vs.* 5 patients), dopamine (12 *vs.* 9 patients), sodium nitroprusside (11 *vs.* 18 patients), and levosemindan (1 *vs.* 5 patients) in the

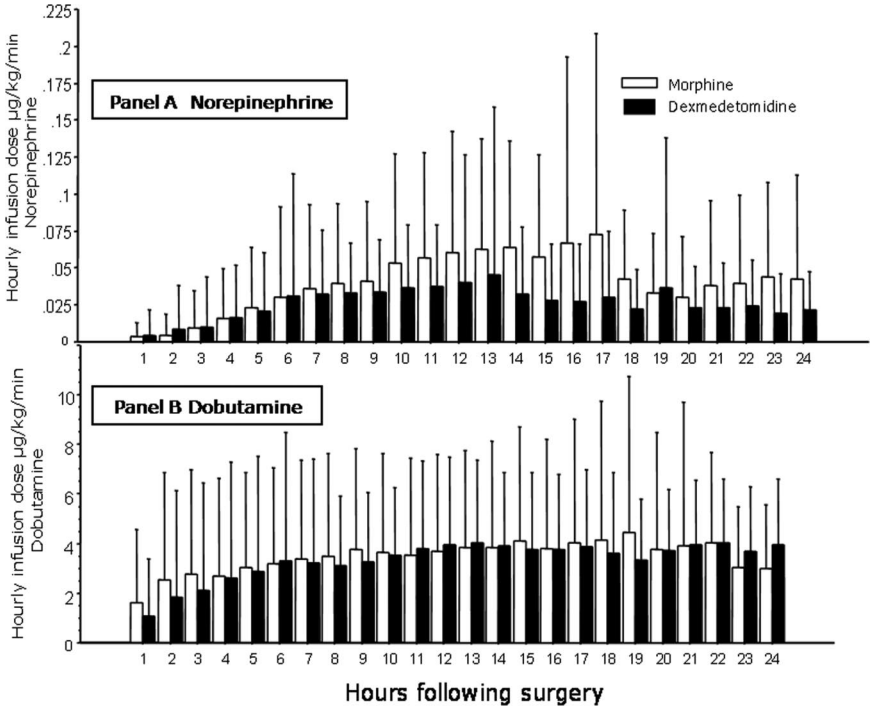

Fig. 5. Hourly dosage of norepinephrine and dobutamine infusions. Hourly (mean ± SD) $\mu g \cdot kg^{-1} \cdot min^{-1}$ of norepinephrine (*A*) and dobutamine (*B*). Using unpaired *t* test showed no difference in the total dobutamine requirements ($P = 0.178$); however, mean ± SD total dose of norepinephrine required was significantly higher in the morphine group ($P < 0.001$).

Table 3. Protocol-defined Adverse Events

Adverse Event, n (%)	Dexmedetomidine (n = 152)	Morphine (n = 147)	*P* Value*
Cardiovascular			
Bradycardia†	25 (16.5)	9 (6.1)	0.006
Systolic hypotension‡	35 (23.0)	56 (38.1)	0.006
Troponin I rise ≥ 3 ng/ml	35 (25.7)	35 (25.4)	0.873
Atrial fibrillation	31 (20.4)	35 (23.8)	0.284
Atrial flutter	1 (0.7)	2 (1.4)	0.487
Ventricular tachycardia	2 (1.3)	5 (3.4)	0.210
Supraventricular tachycardia	3 (2.0)	5 (3.4)	0.343
Ventricular fibrillation	1 (0.7)	0 (0.0)	
Cardiac arrest (all causes)	2 (1.3)	1 (0.7)	0.513
Need for pacing	21 (13.8)	18 (12.2)	0.409
Return to theatre	3 (2)	3 (2.0)	1.000
Reintubation within 5 days	5 (3.3)	4 (2.8)	0.521
Acute kidney injury or failure§	4/149 (2.7)	6/146 (4.1)	0.538
Neurological impairment‖	1/149 (0.7)	1/146 (0.7)	1.000
Postoperative nausea/vomiting#	21/152 (13.8)	25/147 (17.0)	0.522
Blood sugar level > 10 mmols/l	56 (36.8)	70 (47.6)	0.062
Blood transfusion	62/149 (41.6)	72/146 (49.3)	0.199
Any postoperative infection	4 (2.6)	7 (4.8)	0.372
Cessation of study drug	7 (4.6)	9 (6.1)	0.615

* Fisher's exact test; † bradycardia defined heart rate < 55/min; ‡ hypotension defined as 20% reduction in systolic blood pressure < 90 mmHg; § acute kidney injury defined as creatinine > 100% above baseline or new dialysis need; ‖ neurological impairment defined any postoperative impairment that lasts more than 24 hours, excluding delirium or confusion; # defined as requiring at least three doses of medications for nausea/vomiting.

dexmedetomidine *versus* morphine groups. The use and duration of IABP was comparable (table 2).

Adverse Events. Table 3 summarizes adverse events monitored during the course of the study. The most significantly observed difference in cardiovascular events in the dexmedetomidine group was bradycardia ($P = 0.006$) and hypotension in the morphine group ($P = 0.006$). The bradycardia was well tolerated in most patients leading to no increase in pacing, chronotropic agents, or premature cessation of dexmedetomidine.

Discussion

This randomized double-blind study evaluated the use of a highly selective α_2 agonist for postoperative care in cardiac surgery patients older than 60 yr. Although both dexmedetomidine and morphine-based therapy achieved adequate and equivalent analgesia and sedation, this trial demonstrated specific differences, even after a relatively short period of dexmedetomidine treatment. Although the difference in the incidence of delirium failed to reach statistical significance, the observed 42.9% reduction of delirium with dexmedetomidine may be clinically important in concert with the significant reduction in the duration of postoperative delirium. In addition, a significant reduction in the incidence of delirium was seen in a small subgroup of patients with IABP concomitant to dexmedetomidine treatment. Patients managed with dexmedetomidine were more likely to be extubated earlier, and they experienced less systolic hypotension, lower vasopressor requirements, but more bradycardia compared with morphine-based therapy.

The low prevalence of delirium in our study may be the result of exclusion of certain patients. This includes those with dementia and renal impairment. Furthermore, the low level use of benzodiazepines and the use of morphine in this study may have contributed to low transition to delirium, especially because morphine has been shown to have less delirium potential than other narcotics.[27] Nevertheless, the incidence of delirium in the control arm was identical (15%) to that found in patients older than 60 yr in a recent cohort reported by Katznelson.[28] In this study, patients with IABP also had the highest incidence of delirium. A correspondingly low rate of delirium in postcardiac surgery patients was also previously reported by Kazmierski.[29] However, the incidence of delirium shown in the current study is lower than that reported by Maldonado (50% with propofol or midazolam), who also showed a significant reduction in delirium (3%) with dexmedetomidine after cardiac surgery.[30]

Studies in complex medical and surgical ICU patients showed a reduction in the incidence and duration of delirium, and a shorter ventilation time could be achieved when dexmedetomidine was used for longer than 24 h.[31,32]

The pathophysiology of delirium in acute care and the mechanism by which dexmedetomidine can produce a delirium-sparing effect has been comprehensively reviewed by Maldonado[33] and Sockalingam.[34] Our results concur with experience in the general ICU population and confer that dexmedetomidine has an antidelirium effect in the cardiac surgery population. In addition to significant opioid sparing effects, minimal respiratory depression, and central anxiolysis, dexmedetomidine's biologic plausibility as a sedative agent is supported.

Successful extubation after cardiac surgery is a clinically defining event after which de-escalation of dependency and discharge from ICU becomes possible. Wong *et al.* showed that age greater than 60 yr, female gender, urgent surgery, previous infarction, and the use of IABP to be significant predictors of prolonged ventilation after cardiac surgery.[35] An earlier report suggested a potential ventilatory benefit for dexmedetomidine-based sedation after cardiac surgery, where fewer patients required ventilation beyond 8 h.[36] In the current study, dexmedetomidine treatment promoted earlier extubation (log-rank $P = 0.036$). The real benefit was most apparent in patients who needed more than 18 h of ventilation as shown *via* the Kaplan-Meier analysis. A multivariable

analysis showed that the use of IABP in addition to the type of surgery (valve or combined valve/CABG) to be significant predictors of ventilation time. These findings suggest that the maximum benefit from an alternative mode of sedation (dexmedetomidine) may be realized in patients at high risk of delayed extubation.

Dexmedetomidine-based therapy led to a predictable and acceptable hemodynamic and cardiovascular profile. The concomitant bradycardia was not clinically significant, with no associated increase in inotropic or pacing requirements and no premature cessation of dexmedetomidine infusion. Dexmedetomidine-associated bradycardia may have been caused by concomitant use of β blockers and other rate control agents. Furthermore, the hemodynamic profile of dexmedetomidine-treated patients was characterized by significantly less hypotension and vasopressor requirements. The low incidence of hypotension may be the result of omission of dexmedetomidine loading dose.[37]

Our study was designed to mimic everyday practice; therefore, certain limitations were inevitable. Although routine and standard perioperative strategies used in cardiac surgery were implemented to maintain adequate cerebral perfusion, specific monitoring for cerebral perfusion, such as transcranial Doppler and near infrared spectroscopy were not used. Similarly, we did not measure the levels of antiendotoxin core antibody, which would have identified patients with a low antiendotoxin core antibody level at risk of cognitive dysfunction after cardiac surgery.[38] The study was conducted on a single campus, and this may limit the generality of the results. Since CAM-ICU was measured once daily for up to 5 days after surgery, it is possible that patients who became delirious after day 5 may have been missed, though this is unlikely to be significant. In addition, the unidirectional crossover use of open label additional morphine in the dexmedetomidine group, albeit only in a small number of patients, and the perioperative use of midazolam may have had a confounding effect on the study outcomes and in particular on delirium and ventilation time.

Conclusion

After cardiac surgery in patients older than 60 yr, the use of dexmedetomidine did not reduce the incidence of delirium; however, it has been shown to significantly reduce the duration of delirium, promote early extubation, and achieve targeted sedation and adequate analgesia with no increase in hypotension or vasopressor requirements but more bradycardia compared to morphine regimen.

Given that modern cardiac surgery involves patients with different demographics and high risk profile, the choice of postoperative sedative agents may influence clinically relevant outcomes. The results of this study support an appraisal of current and traditional sedation and analgesia practice in cardiac surgery.

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