# Dexmedetomidine and the Reduction of Postoperative Delirium after Cardiac Surgery

José R. Maldonado, M.D., Ashley Wysong, M.S.
Pieter J.A. van der Starre, M.D., Thaddeus Block, M.D.
Craig Miller, M.D., Bruce A. Reitz, M.D.

**Background:** *Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances.* **Objective:** *The authors investigated the effects of postoperative sedation on the development of delirium in patients undergoing cardiac-valve procedures.* **Methods:** *Patients underwent elective cardiac surgery with a standardized intraoperative anesthesia protocol, followed by random assignment to one of three postoperative sedation protocols: dexmedetomidine, propofol, or midazolam.* **Results:** *The incidence of delirium for patients receiving dexmedetomidine was 3%, for those receiving propofol was 50%, and for patients receiving midazolam, 50%. Patients who developed postoperative delirium experienced significantly longer intensive-care stays and longer total hospitalization.* **Conclusion:** *The findings of this open-label, randomized clinical investigation suggest that postoperative sedation with dexmedetomidine was associated with significantly lower rates of postoperative delirium and lower care costs.*
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Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances.[1–4] Postoperative delirium, an acute organic mental syndrome, is reported to affect up to 57% of cardiac-surgery patients.[5,6] The incidence of delirium is rather high in both medically and surgically ill patients,[7,8] and even higher among intensive-care (ICU) patients (up to 80%).[9,10] In addition to causing distress to patients, families, and medical caregivers, the development of delirium, in general, and postoperative delirium, in particular, has been associated with increased morbidity and mortality,[5,10–13] increased cost of care,[12,14] increased hospital-acquired complications,[13] poor functional and cognitive recovery,[11,15,16] decreased quality of life,[13,15,17] prolonged hospital stays,[5,9,11–13,15,17,18] and increased placement in specialized intermediate- and long-term care facilities.[13,15,17] Despite its prevalence and negative clinical impact, delirium is often unrecognized by medical personnel and staff. Several studies have demonstrated that 32% to 84% of delirium patients go unrecognized by physicians (e.g., house staff, attending).[17,19–22] Furthermore, a study conducted at a teaching hospital suggested that once delirium occurs, only about 4% of patients experience full resolution of symptoms before discharge from the hospital.[11] In the same study, it was not until 6 months after hospital discharge that an additional 40% experienced full resolution of symptoms.

To date, no single cause of delirium has been identified. Known risk factors for delirium include advanced age, preexisting cognitive impairment, medications (especially benzodiazepines), sleep deprivation, hypoxia and

Received April 7, 2008; revised May 8, 2008; accepted May 8, 2008. From the Dept. of Psychiatry and Behavioral Sciences, the Dept. of Anesthesiology, and the Dept. of Cardiothoracic Surgery, Stanford University School of Medicine, Stanford, CA. Send correspondence and reprint requests to José R. Maldonado, M.D., Dept. of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Rd., Suite 2317, Stanford, CA 94305-5546. e-mail: jrm@stanford.edu

anoxia, metabolic abnormalities, and a history of alcohol or drug abuse.[23] Patients undergoing major surgery, including cardiac surgery, are at increased risk of developing delirium because of the complexity of the surgical procedure, the administration of intraoperative and postoperative anesthetic and other pharmacological agents, and postoperative complications.[24,25]

This open-label, prospective, randomized clinical trial was designed to investigate the effects of postoperative sedation on the development of delirium in patients undergoing cardiac-valve operations with cardiopulmonary bypass (CPB). We postulated that sedation with dexmedetomidine may be associated with a lower incidence of delirium, given its particular pharmacological properties: it is not a GABAergic agent, and it has no anticholinergic effects; it produces sedation, and promotes a more physiological sleep pattern without significant respiratory depression, and it has been reported to be associated with a decreased need for opioid use. Similarly, our previous clinical experience had demonstrated the usefulness of the adjunct use of $\alpha_2$-agonist agents (e.g., clonidine) with good success in many patients with delirium not responding to more conventional pharmacological treatments (e.g., neuroleptic agents) in a variety of settings, including those with postoperative patients. Previous studies have shown an increased incidence of cerebral dysfunction and slower recovery in patients undergoing open-heart surgery[6,14,26] such as valve replacement (around 50%[27,28]), as compared with coronary-artery bypass graft (CABG; 25%–32%[29–31]). Thus, we decided to include only patients in the highest risk group (i.e., valve surgery). Specifically, we examined whether the use of dexmedetomidine (a selective $\alpha_2$-adrenergic receptor-agonist with sedative, analgesic, and antinociceptive properties) was associated with a lower incidence of delirium when compared with current postoperative sedation practices (e.g., propofol or midazolam).

## METHOD

### Study Design and Participants

All patients meeting inclusion and exclusion criteria admitted to a large, tertiary-care university medical center scheduled for elective cardiac valve operations were eligible for this prospective, randomized clinical trial. Potential participants underwent a preoperative evaluation and neuropsychiatric testing before randomization. Exclusion criteria included a preexisting diagnosis of dementia or schizophrenia, the preoperative use of psychotropic medications, active or recent substance abuse or dependence, age less than 18 or older than 90 years, documented stroke within the last 6 months, evidence of advanced heart block, pregnancy, or anticipated intraoperative deep hypothermic circulatory arrest.

The protocol was approved by the Institutional Review Board (IRB), and written informed consent was obtained from all participants after establishing eligibility. A baseline examination was obtained, and participants were randomly assigned in equal proportions to one of three study arms. Patients were consecutively enrolled with a goal of attaining 30 completing patients per study arm; blocking was used to ensure equal numbers in the three treatment groups. Randomization was performed the evening before surgery by random drawing. The primary endpoint was the proportion of patients in each treatment group who received a diagnosis of postoperative delirium. Secondary endpoints included length of stay in the ICU, total length of hospitalization, and use of postoperative rescue medications.

### Treatment and Procedures

The preoperative evaluation included a determination of subjects' current medications, medical and surgical history, American Society of Anesthesiologists (ASA) classification,[32] alcohol-consumption and substance-use history,[33,34] a psychiatric and neurologic history, and general demographic variables. Baseline mental status and cognitive functioning were assessed with the Mini-Mental State Exam (MMSE)[35] and the Trail-Making Test, Part A.[36]

Anesthesia for the surgical procedure was standardized among all study groups, including induction with etomidate, fentanyl, and rocuronium and maintenance with fentanyl, midazolam, and inhalation agents (e.g., isoflurane, sevoflurane). Operative procedures were performed via median sternotomy in conjunction with cardiopulmonary bypass (CPB). The protocol for CPB (also standardized among all groups) included moderate hypothermia, at temperatures between 28°C and 30°C, flows maintained between 2.0 L/min/mP2P and 2.4 L/min/mP2P, and mean arterial pressure >50 mmHg. Transesophageal echocardiography (TEE) was used routinely for monitoring pre- and postoperative cardiac performance, assessing valvular abnormalities, and monitoring of adequate de-airing during weaning from CPB. During CPB, all subjects were anesthetized with isoflurane (up to 2%). The only difference in management between the three groups occurred at the time of sternal closure. After successful weaning from CPB, patients were started on one of three randomly assigned, postoperative sedation regimens: dexme-

detomidine (loading dose: 0.4 μg/kg, followed by a maintenance drip of 0.2 μg/kg/hour–0.7 μg/kg/hour), propofol drip (25 μg/kg/minute–50 μg/kg/minute), or midazolam drip (0.5 mg/hour–2 mg/hour).

Upon arrival at the ICU, a standardized protocol for postoperative care was implemented for all patients. Infusion rates for all sedative protocols were titrated in order to achieve and maintain a Ramsay Sedation Score[37] of 3 before extubation and 2 after extubation. All patients were extubated when deemed clinically appropriate according to respiratory-care 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 hours. All patients were allowed the following rescue medications: for additional sedation while intubated, subjects received increased doses of the drug they had been randomly assigned to; fentanyl 25 μg–50 μg every hour as needed for pain was the only opiate used in the first 24 hours; ketorolac, hydrocodone, and oxycodone were allowed for pain management after the first 24 hours (Table 1).

If a patient developed delirium, haloperidol ≤5 mg every 2–4 hours was used as needed for agitation not responding to redirection, medical management, and adjustments of the assigned sedative drugs during the first 24 hours after surgery. After the first 24 hours, haloperidol (≤2 mg IV every 6 hours), and lorazepam (for patients not responding to haloperidol alone) ≤1 mg IV every 6 hours were available, as needed, for agitation. Haloperidol and lorazepam were used only after a diagnosis of delirium was established (Table 1).

No morphine or methadone was allowed for analgesia. No other $\alpha_2$-agonist agents were used pre- or postoperatively in the study. All clinical decisions regarding time of extubation, administration of rescue medications (including pain management, neuroleptics, and benzodiazepines), or removal of a patient from the study were made exclusively by the primary treatment team on the basis of the standardized protocol and clinical judgment without influence or input from the research team.

## Follow-Up

Various scales have been developed to assist nonpsychiatric personnel screen for the presence of delirium. The teams that developed these instruments recommend that all patients identified as having delirium by screening instruments (e.g., the Delirium Rating Scale [DRS], the Confusion Assessment Method [CAM], and the Confusion Assessment Method for the Intensive Care Unit [CAM–ICU]) have "a complete clinical evaluation to confirm the diagnosis."[8,38] All of these scales (i.e., the CAM,[8] CAM–ICU,[19] and DRS[39]) have been derived from and validated against the diagnostic criteria established by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV–TR).[40] Therefore, in our study, the presence of postoperative delirium was determined by a neuropsychiatrist, using the "gold standard" for the diagnosis of delirium: diagnostic criteria from DSM-IV–TR; Table 2). Previous studies have determined that the highest incidence

**TABLE 1. Rescue Protocol**

| | Group A: Dexmedetomidine | Group B: Propofol | Group C: Midazolam |
|---|---|---|---|
| Sedation | Dexmedetomidine loading dose: 0.4 μg/kg,[a] infusion: 0.2–0.7 μg/kg/hr | Propofol: 25–50 μg/kg/min | Midazolam: 0.5–2 mg/hr |
| Analgesia | For the first 24 hours postoperatively, only fentanyl was allowed. Thereafter, ketorolac, hydrocodone, and oxycodone were allowed as needed for pain management. | | |
| Delirium | Management:<br>1) Reorientation and redirection by nursing and medical personnel<br>2) Addressing potential underlying causes<br>3) If medications are needed:<br>a. first 24 hours: only haloperidol 0 mg–2mg IV q 6 hours, as needed, for agitation not responding to above.<br>b. After first 24 hours:<br>i. Haloperidol: 0 – 2mg IV q 6 hours, as needed for agitation not responding to above<br>ii. Lorazepam: 0 – 1mg IV q 6 hours, as needed was allowed for agitation not responding to haloperidol | | |

[a] As recommended by the Food and Drug Administration and as instructed by the product insert.

of postoperative delirium occurs during the first 3 postoperative days.[41–43] Thus, the study was designed to capture postoperative delirium in the first 3 days (when it can safely be associated with the postoperative period). If patients developed delirium within the first 3 postoperative days, they were followed by the team psychiatrist until the delirium subsided.

Delirium was assessed daily between 1600 and 1900 hours during the first 3 postoperative days and was diagnosed when symptoms consistent with DSM-IV–TR criteria had been present during the previous 24 hours. This model is similar to that used by numerous other researchers/studies, which used, for example, the Confusion Assessment Method (CAM),[8] the CAM–ICU,[19] or the Delirium Rating Scale (DRS),[39] taking into account the previous 24 hours of data regarding the patient's behavior. The Delirium Rating Scale (DRS)[39] was used as a confirmatory "standardized" criterion for delirium; the Liptzin-Levkoff Criteria[38] were used to determine the subtype of delirium (i.e., hyperactive, hypoactive, or mixed), and a complete neuropsychiatric examination was performed daily. Postoperative Day 1 evaluations were performed on the first day after surgery, with Time Zero being time of sternal closure. The study's research assistant (RA) examined patients each morning between the hours of 0900 and 1200 for secondary objective measures. Daily evaluations consisted of a patient's interview, a review of the nursing record and medical chart, and a review of medications. Mental status and cognitive deficits were objectively measured with the MMSE and Trail-Making Part A to aid the team psychiatrist in the diagnosis of delirium. All patients were followed until discharge from the hospital.

## Statistical Analysis

We performed a per-protocol analysis of the primary outcome variable and secondary outcomes on the 90 patients who received the study intervention. Power calculations revealed that a total of 90 patients, 30 per arm, was needed to detect a difference in proportions of 30% for incidence of delirium (power of 80%; a two-sided $\alpha$ level of 0.05). An analysis of the primary outcome variable and secondary outcomes was performed on the 90 patients who received the study intervention. The primary outcome was also analyzed according to an intention-to-treat (ITT) format including all 118 randomized patients except the 2 patients who expired on the propofol arm. Of the 19 patients who did not receive the study intervention, a blinded retrospective chart review was performed to determine the incidence of delirium.

Means ($\pm$ standard deviation [SD]) were calculated for all continuous variables. Differences between treatment groups were assessed with analysis of variance for parametric continuous variables, and the Kruskal-Wallis test was used for nonparametric continuous variables. When the null hypothesis was rejected, independent *t*-tests were used to determine differences between groups. Proportions were used to describe categorical variables; chi-square and Fisher's exact tests were performed between the dexmedetomidine treatment group and both standard-of-care arms, propofol and midazolam, for the primary outcome. To report overall treatment effect, the absolute risk-reduction (ARR) and number-needed-to-treat (NNT) were calculated along with 95% confidence intervals (CI). Chi-square and Fisher's exact tests were performed on secondary outcome variables. Univariate logistic regression was used to identify statistically significant predictors of postoperative delirium. Individual variables with a p value of $\leq 0.05$ and a priori predictors of postoperative delirium were subjected to a multivariate logistic-regression model.

A cost-analysis was undertaken based on the average cost per day during the study period at our institution. The estimated average daily costs of $700, $1,500, and $2,200 per day were used to calculate the cost of care for patients located on the general-surgical ward, not intubated in the ICU, and intubated in the ICU, respectively. All reported

**TABLE 2. Criteria for Diagnosing Primary Outcome of Delirium**

DSM–IV Diagnostic Criteria for Delirium

I. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment), with reduced ability to focus, sustain, or shift attention.
II. Change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
III. Disturbance develops over a short period of time (usually hours-to-days) and tends to fluctuate during the course of the day.
IV. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general-medical condition.

Reprinted from Diagnostic and Statistical Manual of Mental Disorders, 4th Edition–Revised (DSM-IV–TR), American Psychiatric Association, 2004.

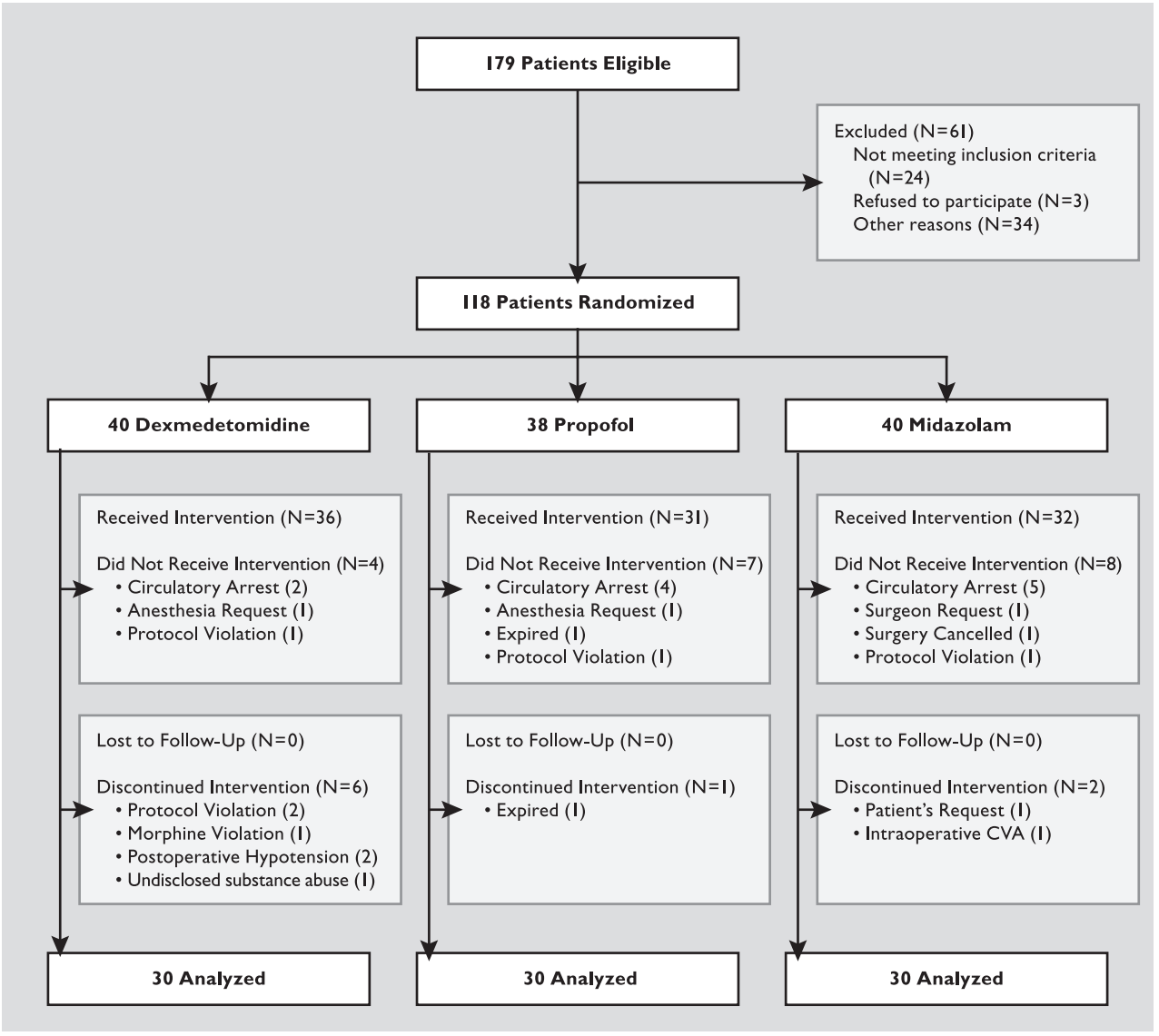
p values are two-sided and have not been adjusted for multiple testing. All analyses were carried out with SAS Version 8.2 (SAS Institute; Cary, NC).

## RESULTS

### Patient Population

A group of 118 patients were randomized: 40 to receive dexmedetomidine; 38, propofol; and 40, midazolam (Figure 1). Two patients expired, both in the propofol group. Neither of these deaths was deemed attributable to the intervention. In total, 28 patients were removed from the study (a 24% dropout rate). The primary treatment team decided on the removal of patients from the study either because of clinical condition or violation of the protocol. The analyses were based on the remaining 90 patients, 30 per treatment arm (Figure 1). The majority of the patients underwent single valve repair or replacement, 33 of the mitral valve (MV) and 32 of the aortic valve (AV); 3 patients had both of these valves replaced. The remaining patients had ascending aortic replacement (9 patients; 6 with AV preservation, 3 with AV replacement); aortic root replacement (9 patients; 7 with AV preservation, 2 with AV replacement); and Ross procedure (3

**FIGURE 1. Flow Diagram of Subjects' Progress for Cardiac-Surgery Patients Undergoing Valve Procedures With Cardiopulmonary Bypass**



patients). A total of 9 subjects underwent CABG as a secondary procedure along with the primary indication for surgery. The treatment groups were statistically similar with respect to demographic and baseline clinical measures, including history of psychiatric diagnoses and baseline MMSE[35] scores and Trail-Making A scores[36] (Table 3).

### Operative and Immediate Postoperative Data

Intra-operative data are presented in Table 4. There were no significant differences between treatment groups with respect to ASA classes, CPB time, aortic cross-clamp time, lowest temperature achieved, length of the surgical procedure, or the length of intra-operative anesthesia. All patients received similar amounts of midazolam and fentanyl during anesthesia in accordance with the protocol described above. The average dose and length of infusions of the study medications in the postoperative period were as follows: dexmedetomidine 0.35 $\mu$g/kg/hr for 13 hours, propofol 26.3 $\mu$g/kg/min for 11 hours, and midazolam 1.5 mg/hr for 10 hours. There were no significant differences between treatment groups in length of postoperative intubation.

### Incidence of Delirium and Postoperative Follow-Up

In the per-protocol analysis, the incidence of delirium for the entire study population was 34% (31/90), well within the reported postoperative standards for this type of surgical procedure.[5] The incidence of delirium for patients on dexmedetomidine was 3% (1/30); for those on propofol, 50% (15/30); and, for patients receiving midazolam, 50% (15/30). The ARR in the incidence of delirium associated with using dexmedetomidine was 47% (95% CI: 28%–66%), corresponding to an NNT of 2.1 patients (95% CI: 1.5–3.6). Patients who developed postoperative delirium experienced significantly longer ICU stays (4.1 versus 1.9 days; $p < 0.001$) and longer total hospitalization (10.0 days versus 7.1 days; $p < 0.001$), as compared with patients not developing delirium. The average age of patients who developed delirium was significantly greater than those who did not (64.9 $\pm$ 15.9 years versus 52.9 $\pm$ 16.1 years; $p < 0.001$; Table 3).

The ITT analysis of the primary outcome revealed an incidence of delirium for the entire study population of 31% (37/118). It showed an incidence of delirium of 10% (4/40) for patients receiving dexmedetomidine, 44% (16/36) for those receiving propofol, and 44% (17/40) for patients receiving midazolam (Table 3).

ICU and total hospital stays were respectively 1.9 and 7.1 days for the dexmedetomidine group, 3.0 and 8.2 days for those receiving propofol, and 3.0 and 8.9 days for patients who received midazolam, respectively. The use of dexmedetomidine was associated with a statistically and clinically significant reduction in fentanyl and total morphine-equivalents when compared with the use of midazolam in the postoperative period. No significant difference in opiate use was seen between dexmedetomidine and propofol patients. There were no differences in proportion of patients who received haloperidol or lorazepam as a rescue medication for delirium (Table 5).

By multiple logistic-regression, postoperative sedation treatment was found to be the most important predictor of delirium, after adjustment for age, sex, baseline MMSE score, and ASA physical status classification (Table 6).

In our study, the average total cost for postoperative care was $7,025 for those in the dexmedetomidine group versus $9,875 and $9,570 for those who received propofol and midazolam, respectively ($p=0.12$; $p=0.07$). The average cost for all patients who developed delirium was $12,965, whereas those who never developed delirium had an average cost of $6,763 ($p=0.004$). These findings are

**TABLE 3. Patient Baseline Characteristics by Postoperative-Sedation Group**

| | Dexmedetomidine (N=40) | Propofol (N=38) | Midazolam (N=40) |
|---|---|---|---|
| Baseline | | | |
| Age, years | 55 (16) | 58 (18) | 60 (16) |
| Gender, male | 26/40 (65%) | 22/38 (58%) | 27/40 (68%) |
| ASA Score (range: 1–4) | 3.3 (0.45) | 3.5 (0.50) | 3.5 (0.57) |
| History of psychiatric treatment | 5/40 (13%) | 5/38 (13%) | 5/40 (13%) |
| Mini-Mental State Exam | 29.6 (0.8) | 29.2 (0.9) | 29.4 (0.9) |
| Trail-Making A (sec.) | 41 (23) | 51 (23) | 42 (14) |

Values are mean (standard deviation), or proportion with (%); MMSE <25 considered cognitive dysfunction.

similar to those of Ebert et al.,[14] who found that the additional cost associated with the development of postoperative delirium in cardiac patients was $6,150 per patient.

## DISCUSSION

This open-label, prospective, randomized clinical trial found that sedation with dexmedetomidine was associated with a significantly reduced incidence of postoperative delirium in patients undergoing cardiac surgery with the use of CPB. The incidence of delirium was 50% in the propofol and midazolam groups, which is consistent with the 57% incidence previously described in this patient population.[5,6] In contrast, the incidence of delirium for patients receiving dexmedetomidine was 3%, corresponding with an ARR of 47%, corresponding to a number-needed-to-treat of 2.1. Similar to previous studies,[14] our

**TABLE 4. Patient Surgical and Intra-Operative Characteristics by Postoperative Sedation Group**

| | Dexmedetomidine (N=30) | Propofol (N=30) | Midazolam (N=30) |
|---|---|---|---|
| Intra-operative variables | | | |
| ASA score (range: 1–4) | 3.3 (0.5) | 3.5 (0.5) | 3.5 (0.6) |
| Cardiopulmonary bypass (min.) | 165 (62) | 162 (57) | 163 (51) |
| Aortic clamp (min.) | 121 (46) | 123 (45) | 122 (44) |
| Lowest temperature (°C) | 29.3 (2.5) | 29.1 (1.8) | 29.4 (4.0) |
| Length of anesthesia (min.) | 404 (107) | 420 (93) | 432 (110) |
| Length of procedure (min.) | 302 (106) | 306 (97) | 330 (108) |
| Midazolam received (mg) | 7.4 (4.0) | 7.2 (2.9) | 7.8 (2.3) |
| Fentanyl received (mcg) | 2,053 (979) | 2,012 (1,126) | 2,296 (1,134) |

Values are mean ± SD, or proportion with (%). ASA: American Society of Anesthesiologists Physical Status Classification System.

**TABLE 5. Selected Postoperative Outcome Variables for Cardiac Patients With Cardiopulmonary Bypass × Intervention Group**

| | Dexmedetomidine (N=30) | Propofol (N=30) | Midazolam (N=30) | Overall p | Dexmedetomidine vs. Propofol | Dexmedetomidine vs. Midazolam |
|---|---|---|---|---|---|---|
| Delirium | | | | | | |
| Incidence of delirium (per protocol) | 1/30 (3%) | 15/30 (50%) | 15/30 (50%) | <0.001 | <0.001 | <0.001 |
| Incidence of delirium (ITT) | 4/40 (10%) | 16/36 (44%) | 17/40 (44%) | <0.001 | 0.001 | 0.002 |
| Delirium, number of days | 2/216 (1%) | 45/276 (16%) | 75/259 (29%) | <0.001 | <0.001 | <0.001 |
| Mean length of delirium,[a] days | 2.0 (0) | 3.0 (3.1) | 5.4 (6.6) | 0.82 | 0.93 | 0.63 |
| Time variables | | | | | | |
| ICU length of stay, days | 1.9 (0.9) | 3.0 (2.0) | 3.0 (3.0) | 0.11 | 0.14 | 0.14 |
| Length of hospital stay, days | 7.1 (1.9) | 8.2 (3.8) | 8.9 (4.7) | 0.39 | 0.42 | 0.12 |
| Intubation time, hours | 11.9 (4.5) | 11.1 (4.6) | 12.7 (8.5) | 0.64 | 0.91 | 0.34 |
| PRN medications | | | | | | |
| Fentanyl, mcg | 320 (355) | 364 (320) | 1,088 (832) | <0.001 | 0.93 | <0.001 |
| Total morphine-equivalents, mg[b] | 50.3 (38) | 51.6 (36) | 122.5 (84) | <0.001 | 0.99 | <0.001 |
| Antiemetic use[c] | 15/30 (50%) | 17/30 (57%) | 19/30 (63%) | 0.58 | | |
| PRN medications for the management of delirium[d] | | | | | | |
| Lorazepam | 1/30 (3%) | 7/30 (23%) | 6/30 (20%) | 0.07 | 0.06 | 0.11 |
| Haloperidol | 0/30 | 3/30 (10%) | 2/30 (7%) | 0.23 | 0.07 | 0.15 |

Values are mean (standard deviation). ICU: intensive-care unit.

[a] of patients who developed delirium.

[b] Sum of average morphine equivalents (fentanyl, oxycodone, and hydrocodone) received in Postoperative Days 1–3.

[c] Number of patients who received dolasetron mesylate and/or promethazine HCl in Postoperative Days 1–3.

[d] Average amount over 3 days. None of these medications was given until a diagnosis of delirium was established.

study suggests that the cost of care nearly doubles in cardiotomy patients who develop postoperative delirium. Given the increased morbidity and mortality associated with delirium and the increased cost of longer hospitalization, these findings may be relevant to the management of cardiac-surgery patients.

The development of postoperative cognitive dysfunction in patients undergoing cardiac surgery has been attributed to the synergistic effect of microemboli, hypoperfusion, and fast rewarming during CPB.[42] It is not clear whether the etiologies of postoperative delirium and neurocognitive decline after cardiopulmonary bypass are related, although they both suggest cerebral dysfunction.[1,2] In a study of ventilated ICU patients, Ely et al.[5] observed that twice as many patients in the delirium group exhibited cognitive impairment at hospital discharge (54.9% versus 26.9% in patients without delirium; $p=0.01$) and were 9 times more likely to be discharged with cognitive impairment than were those in the no-delirium group. Nevertheless, Rothenhäusler et al.[43] did not show any association between the diagnosis of delirium in the ICU and short- or long-term cognitive deficit after cardiac surgery. Long-term follow-up of cognitive functioning was not evaluated in this study and should be considered in future studies to validate the longitudinal clinical significance of our findings.

It has been theorized that patients undergoing intracardiac (valvular) surgery are at higher risk of developing delirium, with the assumption that the embolic load to the brain, consisting of particulate matter and air, is higher than in CABG patients, which makes them potentially more vulnerable for postoperative neuropsychiatric deficits.[44] On the other hand, Van Dijk et al.[45] showed that cognitive outcomes between CABG patients operated with and without the use of CPB were similar, suggesting that factors other than CPB may be responsible for cognitive decline after cardiac surgery. Our findings support the proposal that factors other than CPB, specifically postoperative sedation, may be responsible for mental status changes in cardiac surgery patients.

**TABLE 6. Odds Ratios (95% Confidence Intervals) and p Values for the Association Between A Priori and Statistically Significant Predictors of Postoperative Delirium**

| | Odds Ratio (95% CI)[a] | p |
|---|---|---|
| Midazolam (vs. Dexmedetomidine) | 28.6 (4.7–262.5) | 0.01 |
| Propofol (vs. Dexmedetomidine) | 29.6 (4.8–280.6) | 0.01 |
| Age (increasing 10 years) | 1.3 (1.1–1.5) | 0.01 |
| ASA (increasing 1 point) | 0.98 (0.21–4.5) | 0.82 |
| Sex (male) | 0.76 (0.25–2.3) | 0.62 |

[a] Odds ratios are adjusted for all other variables in the table. ASA: American Society of Anesthesiologists Physical Status Classification System.

At least two sets of theories can be used to explain the fact that patients in the dexmedetomidine group experienced a lower incidence of postoperative delirium. The first suggests that dexmedetomidine has intrinsic "delirium-sparing effects." Several specific characteristics of the drug may account for this effect. First, dexmedetomidine has high and specific receptor selectivity. Studies have suggested that the likelihood of delirium is increased with the number of neurotransmitter pathways disrupted.[1,4,23,46,47] Dexmedetomidine asserts its sedative effects by blocking a single neurotransmitter, norepinephrine, via $\alpha_2$-adrenoceptor binding. The second characteristic is its effect in presynaptic noradrenergic transmission. Changes in the noradrenergic system have been described as potential causative factors in delirium, with increased levels of plasma free-MHPG (3-methoxy-4-hydrophenylglycol) concentration observed in some delirium states.[46,48] Third, dexmedetomidine produces sedation without respiratory depression.[49] Studies have demonstrated that hypoxia and anoxia in the CNS are critical events leading to the biomolecular derangements in delirium.[1,50] Aakerlund and Rosenberg[51] reported lower postoperative oxygen-saturation in post-thoracotomy patients who developed delirium, as compared with patients who did not develop delirium, with the resolution of mental status changes after oxygen supplementation. Fourth, dexmedetomidine lacks clinically significant anticholinergic effects.[52] A strong association has been documented between medications with anticholinergic potential and the development of delirium.[53–55] Fifth, several studies have suggested that postoperative patients sedated with dexmedetomidine have lower opioid requirements—an average of 40% lower.[56,57] This is significant because studies have demonstrated a direct relationship between opiate use and development of delirium.[58,59] Sixth, dexmedetomidine is believed to promote a more physiologic sleep–wake cycle in the ICU setting.[49,60] This is important because sleep deprivation and disruption have been implicated in the onset and perpetuation of delirium.[61] Finally, dexmedetomidine has been shown to have neuroprotective effects[62] in animal models of ischemia[63] and in humans undergoing cardiac surgery.[64]

The second theory suggests that the reason patients had significantly less delirium in the dexmedetomidine

group was not because of its use per se, but because those patients were not exposed to other agents that may have a much greater delirium potential. As suggested by many others, GABAergic agents (i.e., propofol, midazolam) have been implicated in the development and worsening of delirium.[9,65–67] Others have found that agents commonly used for the management of postoperative sedation may contribute to delirium by 1) interfering with physiologic sleep patterns; 2) causing a centrally-mediated acetylcholine-deficient state; and 3) interruption of central cholinergic muscarinic transmission at the level of the basal forebrain and hippocampus.[1,65,68] These may be mechanisms by which midazolam or propofol were associated with higher rates of delirium.[66,67] Nevertheless, given the nature of our study, patients were transferred from intraoperative sedation to one of the study protocols while still in the operating room, after successful weaning from cardiopulmonary bypass. We purposefully chose to use midazolam and propofol as comparators, given that these agents are customarily used in routine medical practice in critical and intensive-care settings, and are both commonly used for postoperative sedation after cardiac surgery. To evaluate propofol or midazolam as causative factors, a placebo group in which both anesthetic agents are avoided must be included. However, this was deemed unsafe by our collaborators and the IRB and may have led the excessive use of other agents by the nursing staff in order to manage patients. There is a trend toward early extubation, and minimizing postoperative sedation, but this was not the goal of our study. The timing and initiation of sedation was aimed at maximal control and safety of patients, as well as an attempt to protect the brain shortly after a stressful episode of open-heart surgery and CPB.[69] This potential neuroprotective effect has been documented with all three sedative agents: midazolam,[70] propofol,[71] and dexmedetomidine.[64]

This is the first prospective study evaluating the potential effectiveness of dexmedetomidine in the reduction of postoperative delirium in adult cardiac-surgery patients. A strength of this study is its homogeneous patient population. Our patients were screened to exclude major preoperative risk factors for delirium not directly related to the surgical procedure itself (i.e., substance abuse, dementia, history of mental-status changes). The baseline variables and demographics of the patients in our study were comparable across the three study groups and are representative of patients having surgery for valve replacement or repair. The evaluated patient population was relatively young, as compared with other studies concerning postoperative delirium, mainly because of the specific referral to our institution of patients with mitral valve prolapse and connective tissue disorders (e.g., Marfan's syndrome). The postoperative medication regimens were standardized across groups to minimize the impact of their use—especially those medications believed to contribute to delirium. Thus, specific agents (e.g., morphine and methadone) were excluded from the protocol so as to further reduce other etiologies of delirium. Fentanyl and oxycodone were used as analgesics because they are associated with a lower incidence of delirium.[59,72]

Previous studies have determined the highest incidence of postoperative delirium to occur during the first 3 postoperative days,[42,43] after which time the onset of delirium could not be clearly attributed to the effects of surgery itself nor distinguished from multiple other factors, such as infections or other secondary medical problems. Evidence also has demonstrated the sine qua non of delirium to be an alteration in the level of consciousness that fluctuates over time.[38] Therefore, patients were independently examined for the development of delirium during the first 3 postoperative days by the study neuropsychiatrist, using DSM-IV–TR criteria. The DRS and MMSE were administered by the RA and used only as a confirmatory measure. Bi-daily measures, thorough chart review, and interview of family members and staff took into consideration any changes in behavior and cognitive status from the time of last observation, a protocol commonly used in previous studies of delirium in medically ill patients.[8] This methodology is similar to that routinely used to examine the frequency of delirium or its duration in the ICU setting.[5,7,8,39]

Since presenting preliminary data of our results,[73] subsequent studies have demonstrated that dexmedetomidine may also reduce the duration of delirium and coma in mechanically-ventilated ICU medical and surgical patients, while providing adequate sedation as compared with lorazepam.[74]

Several limitations to this study should be addressed. First, this was an open-label study. Because of the physical (e.g., propofol is milky white, whereas both dexmedetomidine and midazolam are clear) and pharmacological characteristics (e.g., varied half-lives, titration protocols) of the medications being studied, we were unable to blind the investigators or the ICU personnel. An alternative study design, comparing dexmedetomidine against a placebo, may have allowed for blinding; however, our collaborators and the IRB did not feel placebo to be medically appropriate in this patient population. Strict criteria for the

diagnosis of delirium were utilized, based on the standards set by the DSM-IV–TR; however the possibility of bias, given the open-label study design cannot be eliminated. Second, the dropout rate studying this high-risk population was 24%, (28/118). Nevertheless, statistically, the number of patients removed favored no intervention group. The number of patients discontinued from intervention was highest in the dexmedetomidine group. Two patients were removed from the study because of protocol violation (incorrect titration and length of infusion), and two patients were removed because of hypotension in the immediate postoperative period. These four patients were among the first to receive dexmedetomidine at our institution, when the surgical teams and ICU staff were less familiar with this medication. Careful examination of the subjects' records suggested that the hypotension experienced was more likely a result of hypovolemia, although contribution from medication effect cannot be ruled out. Notably, 11 (39%) of the dropout patients were removed, per exclusion criteria, because of unanticipated deep hypothermic circulatory arrest, with no particular treatment group favored. The high number of patients requiring unexpected deep hypothermia can be attributed to the unique patient population. Many of them had aortic disease, partly because of connective tissue disorders, and it was impossible for the surgeon to identify preoperatively whether the ascending aorta had enough unaffected tissue to be able to clamp the aorta. When this was not the case, the distal anastomosis was made with open (unclamped) aorta, requiring deep hypothermia and circulatory arrest. The intent on the early initiation of sedation was aimed at maximal protection of the brain shortly after a stressful episode of CPB. A total of 5 patients were removed because of protocol violation. A third and final limitation to this study is its lack of intention-to-treat design. Patients who did not receive the study intervention per protocol were not included in the analysis per the original study design. An intention-to-treat analysis may have shown a more conservative effect size. Also, it is unclear whether these findings may be extrapolated to patients at higher risk for delirium, particularly those with baseline cognitive impairment or dementia, who were excluded from this study.

In conclusion, dexmedetomidine administered as a postoperative sedative agent was associated with significantly lower rates of postoperative delirium. Only 2.1 patients need to be treated with dexmedetomidine, rather than propofol or midazolam, for 1 additional valvular cardiac surgery patient to benefit, or not develop delirium. This reduction in the proportion of patients developing delirium may translate to decreases in patient mortality and morbidity, improved patient well-being, shorter hospital stays, and better cognitive functioning. Because delirium is found in a considerable proportion of surgical patients, a reduction of any magnitude in this population could be beneficial for many. These results prompt us to recommend future studies to further evaluate the reduced incidence of postoperative delirium associated with the use of $\alpha_2$ agents, such as dexmedetomidine. If replicated, these findings may have implications for critically-ill, sedated patients in both medical and surgical intensive-care settings.

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