Korean J Thorac Cardiovasc Surg 2014;47:249-254 □ Clinical Research □
ISSN: 2233-601X (Print) ISSN: 2093-6516 (Online) http://dx.doi.org/10.5090/kjtcs.2014.47.3.249

Efficacy and Safety of Dexmedetomidine for Postoperative Delirium in Adult Cardiac Surgery on Cardiopulmonary Bypass

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Background: Delirium after cardiac surgery is associated with serious long-term negative outcomes and high costs. The aim of this study is to evaluate neurobehavioral, hemodynamic, and sedative characteristics of dexmedetomidine, compared with the current postoperative sedative protocol (remifentanil) in patients undergoing open heart surgery with cardiopulmonary bypass (CPB). ***Methods:*** One hundred and forty two eligible patients who underwent cardiac surgery on CPB between April 2012 and March 2013 were randomly divided into two groups. Patients received either dexmedetomidine (range, 0.2 to 0.8 μg/kg/hr; n=67) or remifentanil (range, 1,000 to 2,500 μg/hr, n=75). The primary end point was the prevalence of delirium estimated daily via the confusion assessment method for intensive care. ***Results:*** When the delirium incidence was compared with the dexmedetomidine group (6 of 67 patients, 8.96%) and the remifentanil group (17 of 75 patients, 22.67%) it was found to be significantly less in the dexmedetomidine group ($p < 0.05$). There were no statistically significant differences between two groups in the extubation time, ICU stay, total hospital stay, and other postoperative complications including hemodynamic side effects. ***Conclusion:*** This preliminary study suggests that dexmedetomidine as a postoperative sedative agent is associated with significantly lower rates of delirium after cardiac surgery.

Key words: 1. Postoperative care
2. Dexmedetomidine
3. Complication
4. Thoracic surgery

INTRODUCTION

Postoperative delirium is generally known to develop in up to 57% of cardiac-surgery patients [1]. Given this condition's high incidence rate, the consequences of delirium place a considerable burden on both patients and medical staff because of increased morbidity, higher mortality rates, incomplete functional cognitive recovery, prolonged hospitalization, and increased costs of long-term treatment [2-4]. A number of studies have reported that 32% to 84% of delirium patients go unrecognized by the relevant clinical staff [5], and the causes of postoperative delirium have not yet been identified. The known probable risk factors of delirium after cardiac surgery include advanced age, preexisting cognitive decline, atrial fibrillation, perioperative medications, previous delirium, and other metabolic disorders [6]. Among them, major surgery including cardiac operations may increase the risk of delirium due to intricacy of the surgical procedure,

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Received: July 25, 2013, Revised: November 19, 2013, Accepted: November 21, 2013, Published online: June 5, 2014
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administration of perioperative anesthetic and other pharmacological substances, and postoperative complications [7,8]. We hypothesized that the administration of dexmedetomidine (highly selective and potent α-2 adrenergic agonist with sedative and analgesic properties) may be associated with a lower incidence of delirium by pharmacological action. It produces sedation with modest analgesic and possible anti-delirium effects with minimal respiratory depression [9,10]. The present study was aimed at the investigation of the postoperative sedative effects of dexmedetomidine associated with a lower incidence of delirium, compared with the current postoperative sedative protocol (remifentanil) in patients undergoing open heart surgery with cardiopulmonary bypass (CPB). The primary endpoint was the proportion of patients in each group who developed postoperative delirium. Secondary endpoints included intubation time, length of stay in the intensive care unit (ICU), total length of hospitalization, and use of additional rescue medications.

METHODS

1) Study design and patients

All patients undergoing cardiac surgery are prospectively registered in Konkuk University Medical Center. These registries contain baseline characteristics of patients, perioperative evaluation data, and results or other complications of surgery. All patients fulfilling the inclusion and exclusion criteria and hospitalized for elective open heart surgery were eligible for this study. The study was approved by Konkuk University Medical Center's independent institutional review board, and informed consent was obtained from each patient. A total of 370 patients underwent cardiac surgery from April 2012 to March 2013. We excluded patients who had re-do and emergency surgery, severe pulmonary or systemic disease, left ventricular ejection fraction $<$ 40%, pre-existing renal dysfunction (serum creatinine level $>$ 2.0 mg/dL), and documented preoperative dementia, Parkinson disease, or recent stroke, and who were older than 90 years or younger than 17 years of age. In addition, patients who had psychotropic medications, evidence of progressed heart block, and surgery requiring deep hypothermic circulatory arrest involving thoracic aorta were also excluded. Among them, 142 patients who underwent cardiac surgery on CPB were enrolled in this trial. These eligible patients were randomly assigned to receive either dexmedetomidine (n=67) or remifentanil (n=75).

2) Intraoperative procedures

Anesthesia for the operation was initiated according to the standardized protocol in both groups, including induction with propofol, fentanyl, and rocuronium, and maintenance with fentanyl and inhalation agents like sevoflurane. Surgical procedures were approached via either median sternotomy or right thoracotomy in conjunction with CPB. Right thoracotomy was performed on patients of atrioventricular valve diseases. In thoracotomy, we mostly used the femoral artery and vein or the right internal jugular vein as vascular access for CPB. All patients received standardized CPB management in the same manner. The protocol for CPB included moderate hypothermia (range, 26°C to 30°C) and flows initiated at the rate of 60 mL/kg/min, and was adjusted according to the state of hemodilution and core temperature. Patients were weaned from CPB when their rectal temperature reached 35°C. All patients were monitored with routine cardiac hemodynamic monitoring, including transesophageal echocardiography and pulmonary artery catheter. Bispectral index score (BIS) was also used to estimate the depth of anesthesia by means of an Aspect-3000 BIS monitor. The patients were transferred to, intubated in, and ventilated in cardiovascular ICU (CICU) after surgery.

3) Postoperative administration

Upon return to the CICU, a standardized regimen for postoperative management was followed for all patients; they were started on one of the following two sedative protocols: dexmedetomidine (loading dose, 0.5 μg/kg; maintenance dose, 0.2 to 0.8 μg/kg/hr) or remifentanil (range, 1,000 to 2,500 μg/hr). Infusion rate of drugs was maintained by titration as per the specified protocol to maintain target sedation and adequate analgesia by specially trained nurses who were certified in cardiac intensive care. The efficacy measures for sedation and analgesia were based on the Modified Ramsay Sedation Scale (1–6) and the Numeric Pain Intensity Scale (NPIS: 0–10). We intended to maintain a Ramsay sedation score of 3 (before extubation) and 2 (after extubation).

Additional analgesic agents (e.g., pethidine, morphine, or ketorolac) were applied if NPIS exceeded the grade of 7. The patients in both groups were extubated when clinically appropriate according to respiratory care protocols in CICU. The extubation time as well as the frequency of additional analgesics given was also documented methodically. If a patient developed delirium, haloperidol (5 mg) every 6 hours was administered as needed for agitation and not responding to adjustment of the assigned sedative drugs.

4) Outcome measures

The primary outcome of the study was the proportion of delirium developed during the first 3 days after surgery as determined by the validated delirium instrument, confusion assessment method for ICU (CAM-ICU). The CAM-ICU is the most widely used instrument for diagnosing delirium by medical staff and non-psychiatrists and has been known to have the merits of ease, rapid assessment time, reliability, and validity. CAM-ICU yields a standardized judgment of delirium, which was validated against expert views and Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision [11]. The study was designed to investigate postoperative delirium in the first 3 days because several other studies have reported that the highest incidence of postoperative delirium occurs during the first 3 postoperative days. CAM-ICU was performed once daily between 10:00 am and 12:00 noon (before midday). Abnormal or delirious behavior was recorded every turn-over by individually assigned nurses. Meanwhile, CAM-ICU was not performed in patients who had a Ramsay Sedation Score of 4 or higher (comatose state). Secondary outcomes included duration of ventilator support, length of ICU stay, length of hospital stay, and use of additional rescue medications. Additionally, clinical adverse events were documented in all patients, which were hypotension (defined as SBP less than 90 mmHg), bradycardia (defined as heart rate less than 55/min), re-intubation within 48 hours, and renal failure.

5) Statistical analyses

Statistical analyses were performed with PASW SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as percentages or numbers, and continuous variables are expressed as means with standard deviations. After testing for normality of distribution, continuous variables were compared using the Student t-test. Categorical variables were compared using the chi-square test or Fisher's exact test. All p-values less than 0.05 were considered statistically significant.

Table 1. Types of operation

Variable	Dexmedetomidine group (n=67)	Remifentanil group (n=75)
AVP only	34	22
AVP+MVP	6	13
AVP+coronary artery bypass graft	2	4
MVP only	21	30
MVP+tricuspid annuloplasty	4	6

AVP, aortic valvuloplasty; MVP, mitral valvuloplasty.

RESULTS

A majority of the patients underwent single cardiac valve surgery such as aortic valvuloplasty (AVP) and mitral valvuloplasty, and others including various types of combined valve surgery as well as AVP with coronary artery bypass grafting (CABG) surgery (Table 1). Patients in both groups were statistically similar in terms of the preoperative demographic and baseline characteristics. CPB time, aortic cross-clamp time, intraoperative lowest temperature, the length of operation, and total anesthesia time were not significantly different between the two groups (Table 2). The overall incidence of delirium during postoperative first 3 days was 16% (23 of 142), with 8.96% (6 of 67) occurring in the dexmedetomidine and 22.67% (17 of 75) in the remifentanil group, respectively ($p < 0.05$). In postoperative outcomes, no statistically significant differences were observed between the two groups in the duration of mechanical ventilator support, ICU stay, total hospital stay, and other postoperative complications ($p > 0.05$) (Table 3). However, the number of patients requiring an additional infusion of analgesics such as pethidine and ketorolac was significantly higher in the dexmedetomidine group than in the remifentanil group.

Table 2. Preoperative characteristics and intraoperative details

Characteristic	Dexmedetomidine group (n=67)	Remifentanil group (n=75)	p-value
Age (yr)	51.09±16.10	54.35±13.97	0.199[a]
Gender (male/female)	39/28	40/35	0.559[b]
Body surface area (m^2)	1.68±0.20	1.68±0.17	0.993[a]
New York Heart Association class III & IV	12 (17.91)	12 (16)	0.762[b]
Left ventricular ejection fraction (%)	63.45±9.18	60.45±11.58	0.094[a]
Past history			
Diabetes mellitus	8 (11.94)	5 (6.67)	0.277[b]
Hypertension	16 (23.88)	21 (28.00)	0.577[b]
Present smoking	9 (13.43)	9 (12)	0.798[b]
Chronic obstructive pulmonary disease	2 (2.99)	0 (0)	0.221[c]
Chronic renal failure	4 (5.97)	2 (2.67)	0.421[c]
Cardiopulmonary bypass time (min)	159.55±56.55	173.19±79.56	0.237[a]
Aortic cross-clamping time (min)	94.22±38.40	97.01±45.24	0.698[a]
Lowest temperature (°C)	26.27±0.73	26.27±0.75	0.977[a]
Length of anesthesia (min)	406.87±92.63	403.97±124.51	0.877[a]
Length of operation (min)	344.69±90.63	344.84±119.20	0.993[a]

Values are presented as mean±standard deviation or number (%).
[a]By Student t-test.
[b]By chi-square test.
[c]By Fisher's exact test.

DISCUSSION

The present study evaluated the administration of a highly selective α-2 agonist, dexmedetomidine focusing on cardiac postoperative care. The study concluded that sedation with dexmedetomidine was associated with a significantly reduced incidence of postoperative delirium in patients undergoing cardiac surgery with CPB. In general, cardiac surgery, particularly valve surgery, has a high risk of cardiovascular and other complications with a reported incidence of over 30%. Among others, the occurrence of postoperative cognitive dysfunction in patients undergoing cardiac surgery has been attributed to the synergistic effect of microemboli, hypoperfusion, and fast rewarming during CPB [7,8]. However, it is still obscure whether postoperative delirium or cognitive decline is actually related to CPB or not. As for the type of cardiac surgery, it has been known that patients undergoing valvular surgery are at a higher risk of delirium than CABG patients, which makes them potentially more vulnerable to postoperative neuropsychiatric deficits [12]. Similarly, a majority of the patients considered in this study were cardiac valve surgery patients. The low prevalence of delirium in this study may be justified by the pre-exclusion of certain patients who had diagnosis of dementia or other psychological problems, psychotropic medication, and stroke history.

In addition, choices of sedatives in the postoperative period may be critical for preventing delirium. The highly sensitive α-2-adrenergic agonist, dexmedetomidine, has recently attracted considerable attention due to its ability to provide adequate postoperative sedation and analgesia without producing excessive hypotension or the need for vasopressors, while reducing the risk of delirium after cardiac surgery. Unlike conventional sedatives such as propofol, midazolam, or morphine, dexmedetomidine can produce anxiolysis and sedation without provoking significant respiratory depression. It seems that this respiratory advantage of dexmedetomidine is directly related to postoperative delirium, as other studies have implied that dexmedetomidine's effects on delirium are not simply due to its opioid-sparing properties [13]. Several studies have reported that prolonged periods of intubation increase the risk of delirium by 1.10 to 7.90 times as compared to shorter periods of intubation [14]. Consequently, dexmedetomidine has another potential advantage in that patients may be extubated in the sedated state and that they may be main-

Table 3. Postoperative outcome variables and adverse events

Variable	Dexmedetomidine group (n=67)	Remifentanil group (n=75)	p-value
Delirium			
Incidence of delirium	6 (8.96)	17 (22.67)	0.027[b]
Mean length of delirium (day)	3.5±1.87	3.76±4.13	0.882[a]
Time variables			
Time to extubation (hr)	22.72±26.36	18.60±19.74	0.299[a]
Intensive care unit length of stay (hr)	67.71±48.41	61.25±30.57	0.353[a]
Hospital length of stay (day)	19.96±11.76	18.37±8.45	0.364[a]
Additional rescue medications			
Pethidine HCl	14 (20.9)	6 (8)	0.027[b]
Morphine sulfate	1 (1.49)	1 (1.33)	1.000[b]
Ketorolac tromethamine	15 (22.39)	3 (4.00)	0.001[b]
Additional medications for delirium			
Haloperidol	4 (5.97)	4 (5.33)	0.869[b]
Postoperative adverse events			
Bradycardia (heart rate < 55)	10 (14.9)	8 (10.7)	0.446[b]
Systolic hypotension (systolic blood pressure < 90 mmHg)	12 (17.91)	22 (29.33)	0.111[b]
Atrial fibrillation	5 (7.46)	11 (14.67)	0.175[b]
Atrioventricular dissociation	0	1 (1.33)	1.000[b]
Acute renal failure	2 (2.99)	1 (1.33)	0.602[b]
Cerebrovascular accident	0	2 (2.67)	0.498[b]
Pneumonia	0	1 (1.33)	1.000[b]
Reintubation	1 (1.49)	0	0.471[b]

Values are presented as number (%) or mean±standard deviation.
[a]By Student t-test.
[b]By chi-square test.

tained under sedation as long as necessary until homeostasis is recovered and pain and anxiety are kept under control [15]. These findings presume that the maximum benefit of dexmedetomidine may be realized in patients at a high risk of delayed extubation. A number of previous studies reported that less additional rescue medications for pain control were applied in the dexmedetomidine group, and shorter extubation time was found in this group. However, there were no statistical differences in the duration of intubated state, ICU stay, total hospital stay, and other postoperative complications between the two groups in this study. Besides, the number of patients requiring an additional infusion of analgesics (pethidine and ketorolac) was significantly higher in the dexmedetomidine group unlike the other reports. Therefore, it may be inferred that dexmedetomidine is inferior to remifentanil in terms of the analgesic effect. This is a challenging study evaluating the efficacy and safety of dexmedetomidine with respect to the reduction of postoperative delirium in adult cardiac surgery patients. There are several limitations of this clinical research. First, long-term neurocognitive function was not evaluated in this study and should be included in future research to determine the prognostic significance of delirium in the ICU on long-term cognitive outcomes. Secondly, reasonable rates of dexmedetomidine need to be validated by future extensive randomized studies to confirm the benefits of target agents. Thirdly, the study was conducted in a single medical center; therefore, there are limits to generalizing the results. Lastly, since CAM-ICU was estimated once daily for up to 3 days after surgery, it is possible that patients who appeared delirious after postoperative day 3 may have been missed, although this is likely to be insignificant.

In conclusion, dexmedetomidine administered as a postoperative sedative agent was associated with significantly lower rates of delirium after cardiac surgery with CPB. There

were no statistically significant differences between the two groups in extubation time, ICU stay, total hospital stay, and other postoperative complications including hemodynamic side effects. However, the events requiring additional analgesics were significantly higher in the dexmedetomidine group than in the remifentanil group.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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