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Original Contribution

The association between intraoperative dexmedetomidine and 1 year morbidity and mortality after cardiac surgery: A propensity matched analysis of over 1400 patients☆

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ABSTRACT

Study objective: Dexmedetomidine is widely used during surgery. Recent studies have demonstrated that dexmedetomidine administered perioperatively is associated with lower postoperative mortality and complications in patients undergoing cardiac surgery.

Design: This study was designed to investigate the effects of dexmedetomidine during cardiac surgery in Chinese patients.

Patients/Interventions: We conducted a retrospective review of 1477 consecutive patients who underwent cardiac surgery at our institution. Of these patients, 1077 received dexmedetomidine during their surgery (dexmedetomidine group) and 400 did not (control group). All patients were followed for 1 year. Their short- and long-term outcomes were compared by the inverse-probability of treatment weighted adjustment to reduce treatment selectmen bias. Propensity-score matching yielded two well-matched groups for further comparison.

Main results: After adjusting for differences in baseline risk factors with the inverse probability of treatment weighting, the risk of perioperative mortality (Odds ratio [OR]:1.02; 95% confidence interval [CI]:0.32 to 3.28, $P = 0.97$) and cardiovascular complications were not significantly different between the two groups. After 1 year of follow-up, the two groups showed no differences in mortality (hazard ratio [HR]:0.70; 95% CI 0.28 to 1.73, $P = 0.44$) and major adverse cardiovascular and cerebrovascular events (MACCE) (HR 1.08; 95% CI 0.69 to 1.68, $P = 0.74$).However, postoperative atrial fibrillation was lower in the dexmedetomidine group (OR: 0.53; 95% CI: 0.31 to 0.90, $P = 0.02$).

Conclusions: Dexmedetomidine administered perioperatively reduced postoperative atrial fibrillation, but was not effective in decreasing short and long-term mortality or cardiovascular complications in a Chinese population.

1. Introduction

Dexmedetomidine is a α_2-adrenergic receptor agonist with a highly selective action. It is used predominantly as a sedative or adjuvant anesthetic drug in clinical settings [1–3]. It was first approved for use in humans by the US Food and Drug Administration (FDA) in 1999 for short term sedation in intensive care [4]. Thereafter, many clinical studies have demonstrated its beneficial effects in patients with heart disease in the operating room. Although its use was limited to postoperative sedation [5, 6] and would be to treat arrhythmias in cardiac surgery [7–9], dexmedetomidine often is administrated outside of approved guidelines. It has been described as an ideal medication in the perioperative period of cardiac surgery [10, 11]. The major clinical effects of dexmedetomidine in the perioperative period can be summarized as attenuating hemodynamic responses, providing cardioprotective and antiarrhythmic effects, treating delirium, and procedural sedation.

Despite common adverse effects of bradycardia and hypotension, dexmedetomidine is emerging as an effective therapeutic agent to manage a wide range of clinical conditions with a safe and efficacious

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profile. Multiple studies have reported that dexmedetomidine has a protective effect on specific organs, including the heart, brain, kidney, and lungs [12–16]. However, few studies have explored the impact of α_2 agonists on perioperative and long-term outcomes in patients undergoing cardiac surgery. Recent research has suggested that perioperative use of dexmedetomidine is associated with decreased postoperative mortality up to 1 year and reduced incidence of postoperative complications and delirium in patients who undergo cardiac surgery [17].

However, in these earlier studies most of the enrolled patients were Caucasian [17]. Thus the inability to adjust for racial differences might mask results for specific populations where genetic variants of α_2 adrenoceptors and other proteins in their signaling pathways have been identified. The prevalence of these allelic variants differs substantially among ethnic groups, and these differences could contribute to ethnic differences in responses to $\alpha_2$adrenoceptor agonists [18]. The allele and genotype frequencies of α_{2A}-adrenergic receptor polymorphism were similar to a Caucasian population [19, 20], but not studied in Asian patient papulation. In this study, we retrospectively studied whether the perioperative use of dexmedetomidine was associated with similar improved outcomes in our Chinese patients.

2. Materials and methods

2.1. Patients and study design

This study was conducted retrospectively by examining the records of 1953 patients who consecutively underwent cardiac surgery at from June 1st to September 31st, 2012.

We included all patients who underwent coronary artery bypass graft (CABG) or valvular surgery or combined procedures. The ages of patients' were 18+ years. The exclusion criteria were: emergency surgery, vascular surgery, or congenital heart surgery. 1477 patients met the inclusion criteria and were divided into two groups: those who received dexmedetomidine during the perioperative period (dexmedetomidine group, $n = 1077$) or those who did not (control group, $n = 400$).All the extracted patients were ethnic Chinese population. Data were collected from hospitalization materials and follow-up data.

2.2. Anesthesia management

All patients were intubated after standard induction with midazolam, etomidate, fentanyl/sufentanil, lidocaine and an intravenous injection of rocuronium bromide. A central venous catheter was inserted through the right internal jugular vein. All patients underwent cardiothoracic surgery through a median sternotomy incision. Intraoperative anesthesia management was consistent among our cardiac anesthesiologists, with an institutional standard of a moderate dose of narcotic (fentanyl or sufentanil) supplemented by a volatile anesthetic agent. Ventilation was controlled to an end tidal CO_2 of 35–45 mm Hg by adjusting the tidal volume and respiratory rate. The decision about intraoperative dexmedetomidine use rested solely on the attending anesthesiologist's preference. For patients in the dexmedetomidine group, we initiated the dexmedetomidine infusion at 0.375 to 0.6 $\mu g\,kg^{-1}\cdot h^{-1}$after the central venous catheter was inserted until the operation was completed and maintained dexmedetomidine until extubation in the intensive care unit (ICU). The infusion rate of dexmedetomidine was adjusted according to the patients' hemodynamic changes in response to stimulation. For patients in the control group, no dexmedetomidine infusion was given during or after surgery.

2.3. Definition of outcome events

Perioperative outcomes included in-hospital death from any cause, cerebrovascular accident, myocardial infarction, acute renal failure requiring replacement therapy, atrial fibrillation, and reoperation for bleeding. Long-term follow-up outcomes included death and major adverse cardiac and cerebrovascular events (MACCE), which included stroke, coma, myocardial infarction, cardiac arrests, and heart block.

A cerebrovascular accident was defined as a postoperative image examination showing a new cerebral hemorrhage or embolism lesion with or without related symptoms.

MACCE included the following: permanent stroke– defined as any confirmed neurological deficit with abrupt onset caused by a disturbance in the cerebral blood supply that did not resolve within 24 h. A transient stroke or transient ischemic attack (TIA) was defined as a loss of neurological function that was abrupt in onset but with complete return of function within 24 h. Stroke was diagnosed as a focal or global deficit on physical examination and/or from defects present on imaging studies (computed tomographic scan or magnetic resonance imageing. Coma was defined as unconsciousness occurring secondary to anoxic/ischemic and/or metabolic encephalopathy, thromboembolic event, or cerebral bleeding. Myocardial infarction was defined as the presence of new Q waves in two or more contiguous leads on an electrocardiogram. Heart block was defined as a newly onset block requiring implantation of a pacemaker of any type before discharge.

2.4. Statistical analysis

Continuous data were expressed as the mean ± standard deviation; the *t*-test was used to assess differences in continuous data. Categorical data are displayed as frequencies (percentage), and comparisons were made with chi-square tests. All reported *P*-values are two-sided and $P \leq 0.05$ were considered to indicate statistical significance. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

To reduce the impact of treatment selection bias and potential confounding parameters in the observational study, the propensity score was estimated using multiple logistic-regression analysis without regard to outcomes, and an inverse probability-of-treatment weighting was employed. We used the inverse propensity score as weighting for patients who received dexmedetomidine and the inverse of 1 minus the propensity score for control patients. Model calibration was assessed using Hosmer-Lemeshow statistics, and model discrimination was assessed by C-statistics. A separate propensity score for dexmedetomidine versus non-dexmedetomidine was derived for each comparison. Outcomes were compared using the weighted logistic regression models with the outcome measure as the dependent variable. The odds ratios (OR) for in-hospital outcomes were calculated and 95% confidence intervals were obtained with bootstrap methods. Crude survival was plotted according to the nonparametric Kaplan-Meier method and compared using the log-rank test. Weighted Cox proportional-hazards regression was used to determine the adjusted hazard ratio (HR).

In addition, we compared outcomes with the propensity-score matching to yield well-matched pairs. Propensity score matching was performed using Statistical Analysis Systems software for Windows, version 9.4(SAS Institute Inc., Cary, NC). A predesigned SAS macro program was used for the propensity score algorithm, using an interval score < 0.01 between the 2 groups to define a qualified match. The matched-pairs analysis was performed according to the propensity score for the 400 patients in the control group. They were matched in a one-to-one ratio to patients who received dexmedetomidine. After matched, 399 pairs were exposed. McNemar test was used to assess differences between two groups.

The parameters used in propensity score included age, female, BMI (the body mass index), hypertension, hyperlipidaemia, diabetes mellitus, renal failure, cerebrovascular events, myocardial infarction, ejection fraction, surgical procedure.

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