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CLINICAL TRIAL REPORT

Effect of perioperative administration of dexmedetomidine on delirium after cardiac surgery in elderly patients: a double-blinded, multi-center, randomized study

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Objective: Postoperative delirium (POD) is a serious complication in elderly patients undergoing cardiac surgery. This study was aimed at investigating the effect of perioperative administration of dexmedetomidine for general anesthesia maintenance on occurrence and duration of POD in elderly patients after cardiac surgery.

Methods: One hundred and sixty-four patients were enrolled after cardiac surgery between June 2009 and December 2016. Patients were assigned by a computer-generated randomization sequence in a 1:1 ratio to receive dexmedetomidine general anesthesia maintenance or propofol general anesthesia maintenance. POD was assessed every day with confusion assessment method for intensive care units (CAM-ICU) during the first 5 postoperative days.

Results: There was no significance in incidence of POD between the dexmedetomidine group and the propofol group ($P=0.0758$). In patients treated with dexmedetomidine, the median onset time of delirium was delayed (second day vs first day) and the duration of delirium reduced (2 days vs 3 days) when compared with propofol-treated patients. The dexmedetomidine-treated patients also displayed a lower VAS score and less opiate analgesic consumption. No difference was observed in respect to other postoperative outcomes.

Conclusion: For elderly patients, perioperative administration of dexmedetomidine reduced incidence, delayed onset and shortened duration of POD after cardiac surgery.

Keywords: dexmedetomidine, postoperative delirium, anesthesia, cardiac surgery, elderly patients

Introduction

Delirium is an acute brain disorder, which involves changes in consciousness, attention, cognition and perception.[1] The prevalence of postoperative delirium (POD) in patients undergoing cardiac surgery vary from 20% to 50%.[2,3] Moreover, the incidence increases with age. Patients and their families will be distressed over POD, and it is associated with higher morbidity and mortality, prolonged hospital stay as well as increased health care costs.[4,5]

Anesthesia is one of the predictors of delirium, thus alternatives in anesthesia management might improve delirium-related postoperative outcomes. Analgesia and sedation are important components of postoperative managements, which might affect the incidence of POD as well.[3–5] Inadequate pain control is positively related to the prevalence of POD.[5] However, currently used postoperative analgesics, for example, morphine, are clearly known to promote neurotoxicity.[6,7] It is important to find the

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balance among adequate pain control, analgesia medication choice and delirium reduction.

Dexmedetomidine is a highly selective and potent α2-adrenergic receptor agonist. It was first introduced into the hospital as sedative for ventilated, critical patients.[8] Recent clinical studies have indicated that intraoperative use of dexmedetomidine displayed pro-analgesic and morphine-sparing effect in different types of surgeries.[9–11] The administration of α2-adrenergic receptor agonists has been associated with lower cardiovascular complications in non-cardiac surgeries.[12] Furthermore, dexmedetomidine has long been used for postoperative sedation in patients following cardiac surgeries.[1,13,14] Taken together, dexmedetomidine could provide specific advantages and be an ideal candidate to reduce the prevalence of POD in old patients undergoing cardiac surgeries.

This randomized and double-blinded clinical trial was designed to assess the effect of perioperative administration of dexmedetomidine for general anesthesia maintenance on the prevalence and lasting duration of delirium in elderly patients after cardiac surgery.

Methods

Participants

This was a randomized, double-blind and placebo-controll[illegible] multi-center clinical trial. The study was performed betwee[illegible] June 2009 and December 2016. The study was co[illegible]cted at the Liao Cheng People's Hospital (38 patients), [illegible]e Thir[illegible] Liao Cheng People's Hospital (42 patients) and the [illegible]ffiliate[illegible]Yantai Yuhuangding Hospital of Qingdao Un[illegible]ersity [illegible]patients). The study protocol was approved by t[illegible]Clinical Res[illegible]rch Ethics Committees of Yantai Yuhuan[illegible]ding H[illegible]pitial (2009[illegible]012). This study was conducted in [illegible]ccordance wit[illegible]e Declaration of Helsinki. This study w[illegible] registe[illegible]d in the Chinese Clinical Trial Registry (No ChiC[illegible]-IOR[illegible]/014122). Written informed consent was obta[illegible]d fro[illegible]each pa[illegible]nt. Elderly patients (≥60 years o[illegible]) who[illegible]ere sc[illegible]d[illegible]d for cardiac surgeries were enroll[illegible] into th[illegible]dy. Patients were excluded from this study if they ha[illegible] history of psychiatric diseases; 2) inability to communicate; 3[illegible]revious history of POD; 4) preoperative sick sinus syndrome, severe bradycardia (heart rate <50 beat per minute), second-degree or above atrioventricular block without pacemaker; 5) severe hepatic or renal insufficiency.

Randomization, anesthesia and postoperative sedation/analgesia

Patients were randomized into two groups including dexmedetomidine group and propofol group through biostatistician-generated random numbers in a 1:1 ratio using SAS 12.0 (SAS Institute, Cary, NC). Patients from the both groups received midazolam (0.05 mg/kg), remifentanil (2–5 μg/kg), propofol (1.5–2 mg/kg) and cisatracurium (0.2 mg/kg). Intravenous infusion was switched to a maintenance syringe pump at rate of 50–80 mg/kg/h for propofol, 0.15–0.2 μg/kg/h for remifentanil, with 0.4–0.6 μg/kg/h of dexmedetomidine (DEX group) or without dexmedetomidine (PRO group). A Sedline® monitoring sensor was used to monitor the depth of anesthesia using the Patient State Index (PSI, Masimo, Irvine, CA, USA). Upon admission to the intensive care unit (ICU), patients received propofol (25–50 mg/kg/h) for postoperative sedati[illegible]. Before surgery patients were instructed of the use of [illegible]AS (0, n[illegible]ain, to 100, worst possible pain) and the iv PC[illegible]ump (50 m[illegible]morphine and 8 mg ondansetron in 10[illegible]mL sa[illegible] every [illegible]mp press resulting in a 2 mL infusi[illegible]n).

POD evaluation

As previous s[illegible]as reported, [illegible]OD assessment was performed with the con[illegible]ion assessment method (CAM).[1,20,21] Outcom[illegible]essment w[illegible]performed by research members who[illegible]ere trained prior to the study and not involved in the clin[illegible]al care of p[illegible]ents. The endpoint was the incidence of delir[illegible]n during [illegible]e first five days after surgery. The first assessme[illegible] POD was done ~24 hours after surgery. The ass[illegible]ent was done twice daily (from 8:00 am to 10:00 [illegible]n and from 6:00 pm to 8:00 pm) until the fifth day after surgery. CAM includes a four-step algorithm identifying [illegible]e following: 1) acute onset of mental status changes or a fluctuating course, 2) inattention, 3) disorganized thinking, 4) an altered level of consciousness. Patients were diagnosed to be delirious if both features 1) and 2) were present plus either feature 3) or 4). Diagnosis of delirium was confirmed by the psychiatry consultant. Onset time point and duration of delirium were also monitored.

Statistical analysis

Data were expressed with mean ± SD and analyzed with SAS statistical package. Variable percentages were analyzed with the chi-squared test. The difference (and 95% CI for the difference) between two medians is estimated using the methodology of Hodges-Lehmann. *P*-values <0.05 was considered statistically significant.

Results

Demographic characteristics of the two study groups

Because of personal reasons, there were four patients in the PRO group who did not participate in the assessment. Both groups were similar with respect to demographic data. Overall, all the

Table 1 Baseline demographics and surgical characteristics of the two study groups

	DEX group (n=84)	PRO group (80)
Age, years, mean (SD)	74.7 (7.2)	74.2 (7.7)
Female, n (%)	21 (25)	24 (30)
Preoperative medications, n (%)		
Statins	65 (77.4)	66 (82.5)
Beta-blockers	45 (53.6)	44 (55)
Aspirin	60 (71.4)	58 (72.5)
Angiotensin converting enzyme inhibitors	33 (39.3)	29 (36.3)
Calcium channel blockers	25 (29.8)	29 (36.3)
Antidepressants	12 (14.3)	13 (16.3)
Hemoglobin, g/L, mean (SD)	135.5 (21.2)	137.3 (19.7)
Creatinine, micro-M, mean (SD)	86.6 (23.2)	87.3 (22.9)
Surgery types, n (%)		
Coronary bypass grafting	55 (65.5)	52 (65)
Number of distal anastomoses, median (range)	3 (1–5)	3 (1–5)
Mitral valve	8 (9.5)	10 (12.5)
Aortic valve	50 (59.5)	51 (63.4)
Tricuspid valve	3 (3.6)	2 (2.5)
Replacement ascending aorta	10 (11.9)	11 (13.6)
Hypothermic circulatory arrest	6 (7.1)	6 (7.5)
Cardiopulmonary bypass time, min, mean (SD)	110.8 (25.2)	115.1 (28.9)
Cross-clamp time, min, mean (SD)	84.2 (22.4)	87.7 (24.8)

Abbreviations: DEX, dexmedetomidine; PRO, propofol.

patients from both groups were over 60 years old (62–82), and the information of preoperative medications, comorbidities and surgical characteristics were comparable ($P>0.05$). These data were presented in Table 1 in detail.

The results of POD evaluation

POD was present in 33 of 84 (39.3%) and 21 of 80 (26.3%) in the propofol and dexmedetomidine groups, respectively. In patients treated with dexmedetomidine, the median onset time of delirium was delayed and the duration of delirium reduced when compared with their propofol control (Table 2). In these delirium patients, there was a decreasing trend in extubation time in patients of the dexmedetomidne group when compared with the propofol control group (P=0.00). However, no difference was observed in respect to the ICU stay time and hospital stay time (Table 2).

Postoperative outcomes in the two groups

In both study groups, requirements for inotropic/vasoconstrictor support, permanent pacemaker insertion, blood product transfusion and the length of stay in ICU and the hospital were similarly comparable (Table 3). The 24-hour VAS score and morphine consumption were analyzed by the average of the 5 consecutive days. The range of VAS score and morphine consumption was also provided. VAS pain scores as well as the requirements for opiate analgesic morphine were significantly lower in the patients from dexmedetomidine group as compared with the propofol control group (Table 3).

Postoperative adverse effects

Cardiovascular adverse effects were largely affected by the preoperative disorders and comorbidity, thus, only non-cardiovascular adverse effects were observed in the present study. Overall incidence of non-cardiovascular adverse outcomes were comparable (Table 4).

Discussion

POD is very common complication with high prevalence after surgery, affecting 11%–51% of surgical patients,[15] including those who experienced cardio surgeries. In this article, we observed demedetomidine-based general anesthesia did not reduce the incidence of delirium when compared with propofol-based general anesthesia. Demedetomidine also had no effect on non-cardiovascular postoperative adverse effects. Significant difference was observed on extubation time and requirements for opiate analgesic morphine.

Anesthesia management, such as intraoperative use of dexmedetomidine, has been equivocally implicated in affecting the prevalence of POD. A recent clinical research study performed in the People's Republic of China in a 700 patient randomized, double-blind, placebo-controlled trial, the results showed that prophylactic low-dose dexmedetomidine resulted in an impressive 13% absolute reduction (from 22% to 9%) in the incidence of POD in ICU patients.[16] A more recent

Table 2 Delirium and other postoperative outcomes in patients with delirium

	DEX group	PRO group	*P*-value
Number of delirium (%)	33 (39.3)	21 (26.3)	0.0758
Delirium onset, day, median (range)	2 (1–4)	1 (1–4)	0.0419
Delirium duration, day, median (range)	2 (1–4)	3 (1–6)	0.0238
Extubation time, hour, median (range)	6 (2–24)	10 (2–209)	0.0000
ICU stay time, hour, median (range)	26.8 (22.9–36.8)	29.6 (23.8–35.9)	0.057
Hospital stay time, day, median (range)	20.5 (15.9–34.5)	29.8 (21.2–36.5)	0.1424

Abbreviations: DEX, dexmedetomidine; PRO, propofol.

Table 3 Postoperative outcomes in the two study groups

No. of patients (%)	DEX group (n=84)	PRO group (n=80)	*P*-value
Iontrope/vasoconstrictor use	80 (95.2)	80 (100)	0.4810
Reexploration for bleeding	44 (52.4)	45 (56.3)	0.6191
Permanent pacemaker insertion	6 (7.1)	7 (8.8)	0.7033
Atrial fibrillation	7 (8.3)	6 (7.5)	0.8435
Blood product transfusion	55 (65.5)	57 (71.3)	0.4270
24-hour pain evaluation (VAS score), median (range)	30 (0–80)	35 (0–85)	0.0309
24-hour morphine consumption (mg), median (range)	12 (8–35)	21 (12–40)	0.0222

Abbreviations: DEX, dexmedetomidine; PRO, propofol.

study from the same group failed to observed significant anti-delirium effect of intraoperative used dexmedetomidine in patients following cardiac surgeries.[17] And dexmedetomidine used for ICU sedation also lead to significant reduction in incidence of POD from 15% to 8.5% when compared with morphine, and from 31.5% to 17.5% as compared with propofol after cardiac surgeries.[1,18] However, a recent review suggested no significant benefit could be achieved from dexmedetomidine treatment concerning the incidence of delirium due to the huge variations/heterogeneity of the pooled studies.[19] In this study, we also found no significant benefit of dexmedetomidine treatment for the incidence of delirium. Our results demonstrated that use of dexmedetomidine general anesthesia has only temporary effects on surgical stre

The pathophysiology of delirium after general anesthesia surgery remains unknown, and the potential mechanisms by which dexmedetomidine induces a delirium-sparing effect has been comprehensively reviewed and w interpr d.[1,18] And these mechanisms included im oven of sleep quality after general anesthesia or i ritically ill tients,[20] significant opioid-sparing effects ithou espiratory depression, significant remission o postoperativ fatigue,[9,21] and relieved surgery/anesth a-induced vicious cycle among postoperative pain, fat e an cute stress.[20] All of these positive properties of dex etomidi may have contributed to the ef ct obs ved in the resent study. Although general ane hesia w propofol and postoperative sedation with propofo for cardiac surgery has been a scheduled standard of clinica ractice, together with previous findings, the present study indicated that dexmed midine might be an attractive adjuvant and alternati

A current study found both p stoperative ailty and POD were strongly associat with ior adv e cardiac events (MACE) at 1 yea ter surgery, w le OD was the stronger predictor of M CE tha railty.[22] Other researchers also reported that p operat exercise apacity was strongly associated wit incidence f ssible POD in patients undergoing elective rdiac surgery.[23,24]

Table 4 Non-cardiovascular postoperative adverse effects

No of patients (%)	DEX group	PRO group	*P*-value
Return to operation room	2 (2.4)	2 (2.5)	0.9606
Reintubation within 5 days	1 (1.2)	3 (3.8)	0.2882
Acute kidney injury or failures	2 (2.4)	2 (2.5)	0.9606
Nausea	14 (16.7)	20 (25)	0.1882
Infection	0	0	1.00

Abbreviations: DEX, dexmedetomidine; PRO, propofol.

Li itations

The effects of pr perative exercise capacity on anesthesia was t studied. small sample size was another limitation of this st dditionally, because this is a multiple center st here would be variations in skills of surgeons and nesthesiologists. In the present study, dexmedetomidine was used for general anesthesia, and we have found that his perioperative use of dexmedetomidine delayed onset, and shortened duration of POD in elderly patients following cardiac surgery. The above-mentioned effects produced by dexmedetomidine infusion, including enhanced lowered incidence of delirium and non-delirium complications, may each contribute to these results. However, our study does not provide causal relationships between the various concurrent outcomes.

Conclusion

In conclusion, perioperative administration of dexmedetomidine-based general anesthesia in ICU resulted in the reduced extubation time and requirements for opiate analgesic morphine when compared with propofol-based general anesthesia in elderly patients following cardiac surgeries. However, no significant difference was observed in incidence of POD.

Data sharing statement

We would like to share our deidentified participant data with the permission of the Ethical Committee of Yantai

Yuhuangding Hospital. The individual participant data that underlie the results reported in this study will be shared. Other study related documents will not be provided. The data will be accessible by contacting the corresponding author. Data will be available from date of publication for up to 6 months.

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Disclosure

The authors report no conflicts of interest in this work.

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