CLINICAL STUDY

Anxiety Administered by Dexmedetomidine to Prevent New-Onset of Postoperative Atrial Fibrillation in Patients Undergoing Off-Pump Coronary Artery Bypass Graft

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Summary
This study aims to evaluate the effect of dexmedetomidine (DEX) sedation for relieving anxiety and the incidence of atrial fibrillation (AF) after off-pump coronary artery bypass graft (OPCABG). This randomized, double-blind, controlled trial was conducted on 196 patients who underwent OPCABG in Shandong Provincial Hospital from July 2017 to June 2018. The patients were randomly assigned to two groups, intervention of DEX group and Propofol (PROP) group. Episodes of postoperative AF (POAF) were identified within 5 days after OPCABG. Perioperative anxiety status was assessed using Zung’s Self-Rating Anxiety Scale (SAS). The baseline demographic and surgical characteristics of the population and other outcome variables were evaluated.

We analyzed 62 patients in the DEX group and 61 patients in the PROP group. There was no significant difference in SAS anxiety scores between two groups before surgery ($P = 0.104$), while SAS had significantly after surgery ($P = 0.018$). The incidence of POAF in the DEX group was lower than that of the PROP group (16.1% versus 32.8%, $P = 0.037$), and a total of 30 patients (30/123, 24.4%) manifested POAF after OPCABG. Some univariable predictors of POAF were detected. The conceptual model of mediator analyses showed DEX was not only directly related to POAF but was also indirectly related through the independent effect of anxiety level.

The findings indicated that patients receiving DEX were more likely to have less incidence of POAF, also uniquely showed DEX administration and POAF processes as a function of anxiety status.

Key words: Propofol

Postoperative atrial fibrillation (POAF) is one of the most frequent complications after cardiac surgery. The incidence of POAF after coronary artery bypass grafting (CABG) has been reported to be 20%-60% within 7 days postoperatively.1,2) Previous studies reported that age, resting heart rate, left atrial enlargement, obesity, glycemic fluctuations, obstructive sleep apnea, chronic obstructive pulmonary disease, discontinuation of beta-blockers or Angiotensin-converting enzyme inhibitors, and inflammation are some factors that are involved in the pathophysiology of POAF.3-5) Some prophylactic strategies for the prevention of POAF have been proposed, but they are not routinely implemented in most health care systems because of the lack of convincing evidence and potential risks associated with drug therapies.6)

Anxiety, as one of the factors for psychological vulnerability, appears to be a robust predictor of both POAF and emotional disorders.7) It is associated with worse outcomes after CABG because of the effects of acute stress on blood pressure, myocardial oxygen consumption, and coronary perfusion, which can lead to hyperventilation, arrhythmias, coronary artery spasm, and fatal cardiac events and even mask neurocognitive impairment.7) Tully, et al.8) found that preoperative anxiety increased 2-fold all-cause mortality following CABG. A previous study reported that 45%-50% of patients had preoperative anxiety, which decreased postoperatively to 15%-45%.9) The risk of adverse outcomes, including atrial fibrillation (AF), is increasing in patients who underwent CABG surgery with pre- and post-operative anxiety. Therefore, it is important to per-

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form pre- and postoperative psychological assessment and intervention for individuals at risk for anxiety to improve POAF following CABG.

Dexmedetomidine (DEX), as a highly selective α-2 receptor agonist, has been efficiently and safely applied in perioperative cardiac surgery. DEX could provide effective and safe sedation, reduce delirium and renal and myocardial injury, and facilitate extubation. Narisawa et al. showed that the infusion of DEX during nighttime could facilitate a natural sleep cycle and maintain circadian rhythm and promote respiratory rehabilitation during the daytime. Liu et al. concluded that DEX might be a better choice for sedation in patients after cardiac surgery compared with propofol (PROP). However, the potential factors that contributed to the effect of DEX on preventing POAF were still unclear. Considering the sympathetic inhibition and anxiolytic action of DEX, DEX may reduce the incidence of POAF. Although some studies have evaluated the interaction between DEX and POAF, there is no study empirically incorporating the independent mediating effect of perioperative anxiety status as a predisposing factor for POAF.

This double-blinded prospective randomized controlled trial examined the independent effects of anxiety mediator in the relation of DEX to POAF, and evaluated the value of anxiety as an important predictor of POAF on early outcomes after off-pump coronary artery bypass graft patients (OPCABG). This relation was expected to be mediated by the independent indirect effect of anxiety, which would be evident after adjusting for variables known to occur with DEX and POAF. These data might help to better delineate the relationship of DEX, anxiety, and POAF on the immediate clinical course of patients after OPCABG.

Methods

Study design and population: This randomized and double-blinded clinical trial was conducted at Shandong Provincial Hospital affiliated to Shandong University (Jinan, China) from July 2017 to June 2018. The study was approved by the Ethics Committee of Shandong Provincial Hospital affiliated to Shandong University (No. 2018-201) and registered at chictr.org.cn (ChiCTR-1800014314).

A total of 196 patients with coronary heart disease were enrolled. Inclusion criteria were the patients undergoing OPCABG surgery, age > 18 years, and signed written informed consent. The patients were excluded if they had active myocardial ischemia, cardiac valvular dysfunction, arrhythmias (permanent or paroxysmal AF, supraventricular tachycardia, ventricular arrhythmia, second- or third-degree heart block, and a permanent pacemaker and/or defibrillator), history of psychiatric disorders (schizophrenia, mania, and psychosis), DEX or PROP allergy, liver disease, and were unable to evaluate anxiety scale. Eligible patients were randomly assigned in a 1:1 ratio, with the use of a Web-based randomization system without stratification, to receive either DEX or PROP that was available only shortly before the preparation of the study drug. Data was collected by trained observers who did not participate in patient care and were blinded to the administered drug. The randomization was performed at the last available moment, which could reduce most biases together with the double blindness of the study. In the course of drug application, DEX or PROP was loaded into a lightproof precise filtering infusion apparatus in order to guarantee that nurses were blinded to the drugs. The Shandong Centers for Disease Control and Prevention, as a third party, was responsible for quality control and data management. The School of Public Health of Shandong University participated in statistics.

Operative Technique: All patients received medication, including β-blockers (metoprolol), statins, and non-dihydropyridine calcium channel blockers (CCB) for at least 7 days before OPCABG. The dose of metoprolol was 47.5 mg per day and herbesser was 90 mg per day. All patients underwent electrocardiogram (ECG) and transthoracic echocardiograph pre- and post-surgery. The OPCABG surgery was completed by one group of surgeons. Standard anesthetic induction was performed with intravenous PROP, fentanyl, and vecuronium, which was followed by a standard monitoring of ECG, aortic pressure by arterial catheterization, and pulmonary pressure by a Swan-Ganz catheter. All patients received median sternotomy without cardiopulmonary bypass (CPB). In most cases, the internal thoracic artery was used for grafting to left anterior descending, and the radial artery or saphenous vein was used for Sequential bypass to diagonal branch, left Circumflex, posterior left ventricle branch, and posterior descending artery. From the first day after surgery when tracheal intubation was removed, all patients received β-blockers (metoprolol), statins, and CCB as preoperative medication. Patients did not take any other anti-AF medications as usual. If patients suffered POAF, they were treated for cardioversion or heart rate control with amiodarone or β-blockers.

Psychological assessment: Anxiety status was assessed using Zung's Self-Rating Anxiety Scale (SAS) 3 days before OPCABG and 5 days after OPCABG. The SAS is a 20-item self-report questionnaire to measure the somatic symptoms for cognitive, autonomic, motor, and central nervous system during the past one week. Each question is scored 1-4: 1, a little of the time; 2, some of the time; 3, good part of the time; 4, most of the time. The sums of the raw scores range from 20 to 80, and is converted to an Anxiety Index score by multiplying the sum by 1.25. The Anxiety Index score is used to determine the level of anxiety (25-50, normal range; 50-59, mild anxiety levels; 60-69, moderate anxiety levels; 70-100, severe anxiety levels). If patients were unable to complete the questionnaires because of physical constraints or low cultural level, the nurses would offer assistance in completing the forms without interference with the answers. If patients were suffered delirium to be applied DEX or PROP, SAS evaluation was conducted when patients could be collabrated. In addition, postoperative delirium was evaluated by the confusion assessment method-Intensive Care Unit (CAM-ICU) 5 days after OPCABG.

Intensive Care Unit sedation: Patients with a Riker sedation-agitation score of 3-4 were sedated. The Riker score was monitored hourly during dosage adjustments.
and every 4 hours thereafter. Patients were infused with sufentanil for analgesia at the first 3 days and titrated to a pain score of ≤3 measured by the Pain Assessment Behavioral Scale. Patients received a continuous sedation of DEX or PROP starting from mechanical ventilation after analgesia. The administration rate of DEX was 0.2-1.0 μg/kg/hour, while PROP started at 0.1 mg/kg/hour to a maximum of 3 mg/kg/hour, accompanied by administration of sufentanil at 0.02-0.06 μg/kg/hour. While intubated tracheal intubation, open-label midazolam was permitted to calm violent agitation. Patients were extubated with PaO₂ > 60 mmHg, 40% FiO₂, PaCO₂ < 50 mmHg, and arterial pH > 7.35. After tracheal extubation, most patients were administered with 0.2-1.0 μg/kg/hour DEX or 0.1-2.0 mg/kg/hour PROP only from 8 p.m. to 6 a.m., as assessed by the Riker score. In particular, for getting 6-8 hours of sleep, DEX or PROP dosages might be adjusted several times. In addition, DEX or PROP could be used for more time if patients were agitated or if they had suffered from delirium during the daytime.

**Outcome measures:** All outcomes, except anxiety status and catecholamine concentration, were measured before hospital discharge by reviewing patients’ charts and interviewing the patients. The investigators who conducted outcome assessments were blinded to patients’ groupings. The main outcome variable was the incidence of POAF. POAF was defined as a new-onset episode of AF during hospitalization after OPCABG and recorded in the patients’ medical records, including postoperative cardiology consultation, progress, ECG strips generated after surgery, consultation, progress, ECG strips generated after surgery, and every 4 hours thereafter. Patients were infused with sufentanil for analgesia at the first 3 days and titrated to a pain score of ≤3 measured by the Pain Assessment Behavioral Scale. Patients received a continuous sedation of DEX or PROP starting from mechanical ventilation after analgesia. The administration rate of DEX was 0.2-1.0 μg/kg/hour, while PROP started at 0.1 mg/kg/hour to a maximum of 3 mg/kg/hour, accompanied by administration of sufentanil at 0.02-0.06 μg/kg/hour. While intubated tracheal intubation, open-label midazolam was permitted to calm violent agitation. Patients were extubated with PaO₂ > 60 mmHg, 40% FiO₂, PaCO₂ < 50 mmHg, and arterial pH > 7.35. After tracheal extubation, most patients were administered with 0.2-1.0 μg/kg/hour DEX or 0.1-2.0 mg/kg/hour PROP only from 8 p.m. to 6 a.m., as assessed by the Riker score. In particular, for getting 6-8 hours of sleep, DEX or PROP dosages might be adjusted several times. In addition, DEX or PROP could be used for more time if patients were agitated or if they had suffered from delirium during the daytime.

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**Statistical analysis:** According to the literature, sample size determination was based on an expected 15% occurrence of POAF in the DEX group and an expected 40% occurrence of POAF in the PROP group. At a significance level of 0.05 with a power of 0.80, the resulting sample size was ≥96 patients. Data were reported as mean ± standard deviation for continuous variables and also as statistics and percentages for categorical variables. In univariate analysis, categorical variables were compared using the χ² test or Fisher’s exact test. The repeated-measures analysis of variance (ANOVA) was used to evaluate the changes in anxiety scores and echocardiography examinations. All continuous variables were analyzed using the Mann-Whitney U test. To test the independent effects of anxiety mediators in relation to DEX to POAF, three linear regression models were performed to obtain standardized β-values: Model 1 for DEX and POAF, Model 2 for DEX and postoperative anxiety scores, and Model 3 for the significant relationship of DEX, postoperative anxiety scores, and POAF when sex, body surface area (BSA), preoperative left ventricular diameter (LV), postoperative left ventricular ejection fraction (LVEF), and postoperative suction drainage were considered in the analysis. SPSS version 18 (SPSS Inc., IBM, Armonk, NY, USA) was used for statistical analyses. P < 0.05 was considered statistically significant.

**Results**

**Characteristics of patients:** A total of 196 patients were assessed for eligibility after cardiac surgery (Figure 1). As shown in Figure 1, 62 patients in the DEX group and 61 patients in the PROP group were analyzed. There was no difference in baseline demographic and surgical characteristics between the DEX and PROP groups (Table I).

**Sedation efficacy of DEX and PROP group:** All patients received DEX or PROP for about 3-5 days (median: 4 days). In addition, they received continuous infusion of sufentanil for 3 days, and the cumulative amounts administered over the study period were similar between groups. There were good analgesic and sedation effects, 8.2% versus 9.7% in pain score > 3, and 4.8% versus 8.2% in the Riker score > 5 between DEX and PROP group (Table II).

**Postoperative characteristics of the DEX and PROP groups:** The occurrence of POAF was statistically lower in the DEX group than that of the PROP group (10 (16.1%) versus 20 (32.8%); P = 0.037). Onset of POAF in both the DEX and PROP groups was 3 days post-surgery (IQR, 2, 3 and IQR, 3, 4, respectively) (P = 0.076). The incidence of delirium was 4.8% in the DEX group and 14.8% in the PROP group (P = 0.075). AF post-surgery was 178.2 ± 29.1 ng/L in the DEX group and 188.14 ± 24.5 ng/L in the PROP group (P = 0.061, Table III).

**Risk factors to POAF:** As shown in Table III, a total of 30 patients (30/123, 24.4%) were identified as manifesting POAF, which were used to assess the risk factors of POAF. The descriptive features and univariable predictors of POAF are shown in Table IV. The univariate logistic regression showed that DEX administration was associated with the development of POAF (odds ratio [OR] 2.537, 95% confidence interval [CI] 1.071-6.009, P = 0.034). BSA (OR 0.191, 95% CI 0.039-0.998, P = 0.034), NYHA class (OR 1.975, 95% CI 1.069-3.649, P = 0.03), postoperative suction drainage (OR 1.003, 95% CI 1.001-1.005, P = 0.005), LA after surgery (OR 6.579, 95% CI 1.987-21.775, P = 0.002), LVEF after surgery (OR 0.873, 95% CI 0.815-0.934, P = 0.000), AF after surgery (OR 1.016, 95% CI 1.001-1.031, P = 0.041), mechanical ventilation time (OR 1.085, 95% CI 1.011-1.031, P = 0.023), postoperative anxiety (OR 3.337, 95% CI 1.8-6.188, P = 0.000), and postoperative pain (OR 4.121, 95% CI 1.949-8.713, P = 0.000) were associated with POAF.

**Perioperative anxiety and POAF:** All patients completed the valid Zung’s SAS questionnaires (Cronbach’s α =
As shown in Table V, there is no significant difference in SAS anxiety scores between the two groups before surgery ($P > 0.05$). The most common clinical manifestations reported by patients were “I feel more nervous and anxious than usual,” “I get upset easily or feel panicky” or “I cannot fall asleep easily and get a good night’s rest.” However, SAS anxiety scores in both groups were lower after operation than that before operation. In addition, there was significant difference in postoperative anxiety between the DEX and PROP groups ($47.5 \pm 9.2$ versus $51.2 \pm 9.1$, $P = 0.018$). At this time, the most common clinical manifestations were “I am bothered by headaches neck and back pain,” “I feel weak and get tied easily,” or “I am bothered by stomach aches or indigestion.” In the PROP group, sleep disorders were widespread.

**Perioperative DEX, anxiety and POAF:** The initial analysis showed that DEX administration was closely related to anxiety scores and POAF. Conceptual model of mediator analyses showed that DEX was not only directly related to POAF but also indirectly relate through the independent effect of anxiety levels (Figure 2). Table VI explicitly shows that DEX is indirectly related to POAF through the independent effect of anxiety of the mediator. Model 1 shows the association between DEX and POAF without anxiety. Model 2 shows the association between DEX administration and postoperative anxiety scores.
Table I. Baseline Demographic and Surgical Characteristics of the Study Population

| Characteristics          | DEX Group (n = 62) | PROP Group (n = 61) | P-value |
|--------------------------|-------------------|--------------------|---------|
| Age (years)              | 64.6 ± 8.2        | 66.2 ± 6.3         | 0.208   |
| Gender, female [n, (%)]  | 17 (27.4%)        | 23 (37.7%)         | 0.847   |
| BSA                      | 1.854 ± 0.156     | 1.816 ± 0.161      | 0.183   |
| Medical history           |                   |                    |         |
| HTN [n, (%)]             | 40 (64.5%)        | 39 (63.9%)         | 1.000   |
| DM [n, (%)]              | 29 (46.8%)        | 28 (45.9%)         | 1.000   |
| RF [n, (%)]              | 2 (3.2%)          | 1 (1.6%)           | 1.000   |
| AMI [n, (%)]             | 10 (16.1%)        | 10 (16.4%)         | 1.000   |
| COPD [n, (%)]            | 7 (11.3%)         | 6 (9.8%)           | 1.000   |
| Cerebral infarction      | 6 (9.7%)          | 6 (9.8%)           | 1.000   |
| The number of bypass      | 4 (4, 5)          | 4 (4, 5)           | 1.000   |
| Euroscore                | 8 (5.75, 9)       | 8 (6.8, 5)         | 0.713   |
| NYHA class               |                   |                    | 0.837   |
| I                        | 9 (14.3%)         | 11 (18.0%)         |         |
| II                       | 38 (61.3%)        | 33 (54.1%)         |         |
| III                      | 14 (22.6%)        | 15 (24.6%)         |         |
| IV                       | 1 (1.6%)          | 2 (3.3%)           |         |
| Before surgery           |                   |                    |         |
| LA (cm)                  | 3.78 ± 0.34       | 3.84 ± 0.36        | 0.338   |
| IVS (cm)                 | 1.00 ± 0.15       | 1.02 ± 0.14        | 0.406   |
| LV (cm)                  | 5.00 ± 0.55       | 4.99 ± 0.46        | 0.463   |
| LVEF (%)                 | 57.0 ± 6.3        | 56.2 ± 6.4         | 0.929   |
| DA (ng/L)                | 136.6 ± 20.2      | 134.9 ± 19.4       | 0.152   |
| AD (ng/L)                | 185. ± 27.9       | 186.3 ± 35.3       | 0.925   |
| NE (ng/L)                | 196.2 ± 32.4      | 186.3 ± 35.3       | 0.081   |

BSA indicates body surface area; HTN, hypertension; DM, diabetes mellitus; RF, renal failure; AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; CI, cerebral infarction; NYHA, New York Heart Association; LA, left atrial diameter; IVS, interventricular septal thickness; LV, left ventricular diameter; LVEF, left ventricular ejection fraction; DA, dopamine; AD, adrenaline; and NE, norepinephrine.

Table II. Details of Administration and Sedation Efficacy in the DEX and PROP Groups

| Infusion rate (μg/kg/hour or mg/kg/hour) | DEX (n = 62) | PROP (n = 61) |
|-----------------------------------------|-------------|--------------|
| During tracheal intubation               | 0.55 (0.4, 1.0) | 0.85 (0.5, 2.0) |
| After tracheal intubation               | 0.4 (0.3, 0.8)  | 0.6 (0.4, 1.5)  |
| All cumulative of midazolam (mg)        | 5 (0,10)     | 5 (0,10)     |
| Duration of study drug (days)           | 4 (3,5)      | 4 (3,5)      |
| Riker score                             | 1-2 [n, (%)] | 9 (14.5%) | 14 (23%) |
|                                        | 3-4 [n, (%)] | 50 (80.6%) | 42 (68.9%) |
|                                        | 5-7 [n, (%)] | 3 (4.8%) | 5 (8.2%) |
| Pain score                              | > 3 [n, (%)] | 5 (8.2%) | 6 (9.7%) |

Summary statistics are presented as % of patients, medians [Q1, Q3].

Discussion

Previous studies showed that higher levels of anxiety were directly related to physical comorbidities and the incidence of POAF in patients who experienced OP-CABG. In addition, some studies have shown that DEX gives adequate sedation and could facilitate recovery from cardiac surgery, decrease anxiety, and improve cardiovascular stability. However, it is still controversial whether DEX could decrease POAF for patients after cardiac surgery. Our study showed that DEX administration duration of ICU stay was significantly more reduced POAF than PROP administration. Furthermore, the effect of DEX administration on POAF was complex, not neatly explained by changes in catecholamines, but at least partially based on the independent effect of anxiety. Compared with other studies, the design of this study was farther optimized by
several factors. First, the exclusion criteria of patients could eliminate the pathological basis of AF. Second, the OPCABG could exclude myocardial damage of CPB. Third, no matter before or after surgery, patients were pressed formulary standard medication of metoprolol and statins, which benefit controlling arrhythmia and excluding drug affects. Fourth, this study uniquely contributed empirical data of catecholamine in neurohumoral factors related to DEX and POAF. It revealed that whether DEX could impact on the change of hormonal levels and the speculated the theory of DEX affecting on POAF. Fifth, we redefined the DEX intervention time. The DEX intervention time was from the revival of ICU admission up to 5 days after surgery, which significantly extended the application time of DEX and achieved better sleep.

Anxiety accompanied by POAF was associated with postoperative changes of autonomic arousal symptoms, cognitive interpretation of physical symptoms, mental stress, and circadian disorder. Hansson reported that mental stress was the most commonly recalled “trigger” of arrhythmia among patients with idiopathic paroxysmal AF, and more than 50% of patients with onset arrhythmia had anxiety. This finding did not indicate that anxiety was predictive of AF but it indicated that anxiety was closely associated with concurrent POAF. Whether improving anxiety status was beneficial to decrease the incidence of POAF was still a vacancy of study on it. Therefore, our study focused on the changes of anxiety and incidence of POAF, and firstly compared the anxiety after DEX administration with anxiety after PROP administration in perioperative period. The SAS showed that there was a mild level of preoperative average anxiety, which could be understood as the psychological reaction of surgery rather than body reaction considering the SAS assessed 3 days before OPCABG. After surgery, the SAS in the two groups dropped, and there were statistical differences between the DEX and PROP group. In addition, the patients in the PROP group had more severe sleep disorder than the patients in the DEX group, which means DEX had an advantage in sedation than PROP through on SAS scale. In an experimental setup, DEX was confirmed to induce a sedative response similar to natural sleep. Chryssostomou reported that for patients who underwent congenital heart disease surgery, DEX had an antiarrhythmic property during the perioperative period. Robert reported DEX could reduce the development of delirium and facilitate remembrance of ICU experiences. Xu reported a propensity-matched analysis of over 1400 patients that DEX sedation was more effective in reducing AF after cardiac surgery than not used. However, Sairaku suggested that although DEX may depress the sinus and atrioventricular nodal function, it may not reduce the AF inducibility. Ai analyzed 703 patients who underwent lung cancer surgery and concluded that the intraoperative use of DEX was not associated with the reduction of the incidence of POAF. Therefore, such controversies indeed encouraged researchers to further improve and standardize DEX administration. Our study suggested that long intervention time of DEX (such as 4-5 days at night) postoperative anxiety levels significantly dropped and the incidence of POAF decreased.

In this study, we found that BSA, NYHA Class, DEX, postoperative suction drainage, LA and LVEF after surgery, AF after surgery, preoperative anxiety, postoperative anxiety, and mechanical ventilation were correlated to POAF, while other variables were not related to POAF.
predicting POAF. Furthermore, this study uniquely con-


tably along with the appearance of POAF, but preoperative

In addition, it was understandable that postoperative anxi-

structural remodeling, could lead to an increase in POAF. The

I n t H e a r t J

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P

AMI [ ]

DM [ ]

RF [ , %] 3 (3.2%) 0 0.162 0 / 0.999

AMI [ , %] 13 (14.0%) 7 (23.3%) 0.115 0.534 0.191-1.494 0.231

COPD [ , %] 9 (9.7%) 4 (13.3%) 0.287 0.696 0.198-2.448 0.575

The number of bypass

Euroscore

NYHA Class

I

17 (18.3%) 3 (10.0%)

II

56 (60.2%) 15 (50.0%)

III

19 (20.4%) 10 (33.3%)

IV

1 (1.1%) 2 (6.7%)

Before surgery

LA (cm) 3.74 (3.57, 3.97) 3.84 (3.59, 4.08) 0.027 3.013 0.957-9.481 0.059

LV (cm) 4.95 ± 0.42 5.14 ± 0.69 0.041 1.994 0.905-4.397 0.087

LVEF (%) 60 (55, 61) 58.5 (50, 61) 0.056 0.952 0.896-1.012 0.116

DA (ng/L) 138.4 ± 22.9 142.0 ± 20.1 0.174 1.009 0.990-1.028 0.349

AD (ng/L) 184.1 ± 32.0 194.4 ± 31.5 0.048 1.011 0.998-1.024 0.099

NE (ng/L) 192.0 ± 32.9 189.0 ± 27.5 0.329 0.997 0.984-1.010 0.656

DEX 52 (55.9%) 10 (33.3%) 0.016 2.537 1.071-6.099 0.034

Reintubation

1 (1.1%) 1 (3.3%) 0.200 3.172 0.192-52.329 0.42

Acute renal failure

1 (1.1%) 1 (3.3%) 0.200 3.172 0.192-52.329 0.42

Postoperative suction drainage (mL) 485.4 ± 174.4 609.0 ± 246.4 0.001 1.003 1.001-1.005 0.005

Hypotension

5 (5.4%) 1 (3.3%) 0.327 0.607 0.068-5.41 0.655

Bradycardia

3 (3.2%) 1 (3.3%) 0.489 1.034 0.104-10.334 0.997

Delirium

8 (8.6%) 4 (13.3%) 0.226 1.635 0.455-5.868 0.451

Respiratory depression

4 (4.3%) 3 (10.0%) 0.122 2.472 0.521-11.737 0.255

CRP 42.4 ± 22.5 41.3 ± 21.4 0.811 0.998 0.979-1.017 0.809

After surgery

LA (cm) 3.71 ± 0.32 3.95 ± 0.39 0.000 6.579 1.987-21.775 0.002

LV (cm) 4.86 ± 0.47 5.07 ± 0.63 0.027 2.341 0.976-4.664 0.058

LVEF (%) 60 (55, 60) 50 (45, 60) 0.000 0.873 0.815-0.934 0.000

DA (ng/L) 130.3 ± 21.0 137.9 ± 19.7 0.043 1.017 0.997-1.037 0.090

AD (ng/L) 179.8 ± 25.6 191.7 ± 29.9 0.019 1.016 1.001-1.031 0.041

NE (ng/L) 190.2 ± 32.2 197.6 ± 31.1 0.121 1.008 0.995-1.021 0.241

Preoperative anxiety

50.6 ± 11.8 59.7 ± 11.8 0.000 3.337 1.8-6.188 0.000

Postoperative anxiety

47.5 ± 8.7 55.4 ± 6.2 0.000 4.121 1.949-8.713 0.000

Mechanical ventilation time (hours)

11 (8, 13) 10 (5, 25) 0.007 1.085 1.011-1.164 0.023

ICU study time (days)

3 (3, 4) 3 (3, 4) 0.456 0.592 0.857-1.147 0.91

AF indicates atrial fibrillation, OR, odds ratio; POAF, postoperative atrial fibrillation; CPR, C-reactive protein; ICU, intensive care unit; BSA, body surface area; HTN, history of hypertension; DM, diabetes mellitus; RF, renal failure; AMI, Acute myocardial infarction; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; LA, left atrial diameter; LV, left ventricular diameter; LVEF, left ventricular ejection fraction; DA, dopamine; AD, adrenaline; and NE, norepinephrine. Summary statistics are presented as % of patients, means ± SD, or medians [Q1, Q3], respectively, for factors, symmetric continuous variables, and skewed continuous variables. *Comparison of descriptive analysis; † Single factor regression analysis results.

Some variables, such as NYHA class and LA and LVEF after surgery, representing severe cardiac pathological structural remodeling, could lead to an increase in POAF. In addition, it was understandable that postoperative anxiety along with the appearance of POAF, but preoperative anxiety is closely related to POAF as well. We proposed a bold hypothesis that there was prone to anxiety tend in POAF susceptible population before the onset of symptoms, and preoperative anxiety might be a parameter for predicting POAF. Furthermore, this study uniquely contributes empirical data to support conceptual and theoretical models of DEX and POAF. Specifically, it indicated that DEX was not only directly related to POAF but also to POAF process, which was partly explained by the effect of postoperative anxiety status. This effect was beyond the effects of BSA, NYHA Class, postoperative suction drainage, LA and LVEF after surgery, AD after surgery, preoperative anxiety.27) Thus, after DEX administration to relieve anxiety, it appears to be particularly relevant in explaining the greater reduction of POAF, which is
Table V. Anxiety Assessment before and after the Surgery

| SAS scores | DEX Group (n = 62) | PROP Group (n = 61) | P-value |
|------------|-------------------|--------------------|---------|
| Preoperative anxiety | $51.0 \pm 13.5$ | $54.4 \pm 9.2$ | 0.104 |
| Normal [n, (%)] | 20 (32.3%) | 17 (27.9%) |
| Mild [n, (%)] | 24 (38.7%) | 26 (42.6%) |
| Moderate [n, (%)] | 17 (27.4%) | 17 (27.9%) |
| Severe [n, (%)] | 1 (1.6%) | 1 (1.6%) |
| Postoperative anxiety | $47.5 \pm 9.2$ | $51.2 \pm 9.1$ | 0.018 |
| Normal [n, (%)] | 30 (48.4%) | 20 (32.8%) |
| Mild [n, (%)] | 30 (48.4%) | 31 (50.8%) |
| Moderate [n, (%)] | 2 (3.2%) | 10 (16.4%) |

SAS indicates Self-Rating Anxiety Scale; DEX, dexmedetomidine; and PROP, propofol.

Table VI. Joint Association between Postoperative Anxiety Scores, DEX Administration, and POAF

| Relationship | $\beta$ | $P$ |
|--------------|--------|-----|
| Model 1 | DEX $\rightarrow$ POAF | 1.543 | 0.018 |
| Model 2 | DEX $\rightarrow$ Postoperative anxiety | 1.437 | 0.031 |
| Model 3 | DEX, Postoperative anxiety $\rightarrow$ POAF | 1.373 | 0.03 |
| Postoperative anxiety | 0.143 | 0.001 |
| Sex | 1.637 | 0.032 |
| BSA | 5.394 | 0.019 |
| Preoperative LV | $-2.682$ | 0.009 |
| Postoperative LVEF | $-0.297$ | 0 |
| Postoperative suction drainage | 0.004 | 0.022 |

$\beta$ indicates longitudinal regression coefficient; DEX, dexmedetomidine; POAF, postoperative atrial fibrillation; BSA, body surface area; LV, left ventricular diameter; and LVEF, left ventricular ejection fraction.

Figure 2. Conceptual model of mediator analyses. A: specific direct effects of X on M; B: specific direct effects of M on Y; and C: direct effect of X on Y, controlling for M.

Partially consistent with hypotheses. However, when considering the variables of anxiety, the incidence of POAF was dropped at about 11%. Thus, the patients who had DEX administration might report lower levels of rhythm change when in the context of affect lessen of anxiety. The findings have several clinical implications: first, in the context of high incidence of POAF, it is important to assess one’s interpretation of anxiety rather simple medical therapy; second, for DEX administration, it is important to assess anxiety status produced by the effects POAF. In generally, under the premise of safe dosage, DEX dosage should be adjusted on the basis of anxiety status, which may be helpful in preventing POAF.

This study has several limitations. First, some other sedative drug interventions were unavoidable. We did not evaluate the effects of related drugs (morphine, chlorpromazine) on DEX or PROP. During tracheal intubation, midazolam was injected for rapid tranquilization. Morphine or chlorpromazine was applied to the patients who had delirium after having received the maximum dosage of...
DEX or PROP. Second, the number of patients included in this study was small. In order to exclude the influence of cardiac pathology, such concomitant valvular diseases were not included. Third, the patients in our region possess the characteristic of being overweight and mainly distributed in 60-70 years old. Therefore, the present study showed BSA was related to POAF, but whether lose weight is beneficial to decrease POAF is not clear and may be an interesting research direction. Although, in this study, age distribution was too restrictive, there was no distinct effect on clinical characteristics of POAF.

Conclusions

In general, the findings indicated that patients receiving DEX were more likely to have less incidence of POAF, also uniquely showed DEX administration and POAF processes as a function of anxiety status. In addition, this study showed further conceptual understanding and clinical application of DEX administration, how it relates to POAF, and provided the assessment and treatment for emotionally vulnerable cardiac surgery patients.

Disclosure

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of Shandong Provincial Hospital affiliated to Shandong University (No. 2018-201) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest: The authors declare that they have no conflict of interest.

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