Treatment of Supraventricular Tachycardia in Patients with Non-Cardiac Surgery by Dexmedetomidine During the Perioperative Period. A Randomized Trial

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Research article

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Abstract

**Background:** Previous studies have shown that application of dexmedetomidine (Dex) combined anesthesia during surgery can significantly reduce cardiovascular system complications and mortality of patients with cardiac disease during the perioperative period. The aim of this study was to explore the therapeutic effect of Dex on perioperative supraventricular tachycardia (SVT) in adult patients with non-cardiac surgery.

**Methods:** Forty-six patients with SVT undergoing elective non-cardiac surgery were randomly divided into two groups, intravenously infused Dex (Dex group, 1.0 µg/kg) or midazolam (midazolam group, 0.06 mg/kg) for 10 minutes, respectively. The observation indexes containing the treatment efficiency of SVT, heart rate (HR) and heart rate variability (HRV) including normalized low frequency power (LFnorm), normalized high frequency power (HFnorm) and LFnorm/HFnorm were recorded.

**Results:** Treatment rates of SVT were 21/23 (91.3%) in Dex group vs 2/23 (8.7%) in midazolam group ($P<0.001$). In Dex group, LFnorm and LFnorm/HFnorm were decreased, and HFnorm were elevated and HR were decreased after twenty-three patients infused Dex ($P<0.05$). However, there was no difference for HFnorm, LFnorm and LFnorm/HFnorm in midazolam group ($P>0.05$).

**Conclusion:** Perioperative use of dexmedetomidine has a significant therapeutic effect for SVT, and its mechanism is related to adjust cardiac autonomic nervous system and has no obvious connection with sedation.

**Trial registration:** This trial was registered at ClinicalTrials.gov. registry number: NCT04284150 on February 13, 2020.

Background

Supraventricular tachycardia (SVT) is a common arrhythmia in the perioperative period, which is associated with adverse stimulus such as cardiovascular risk factors, emotional tension, hypoxia, CO$_2$ accumulation, hypokalemia, and pain [1, 2]. Antiarrhythmic drugs, including amiodarone, digoxin, adenosine, verapamil and so on, have been considered the first-line agent in SVT [3–5]. Many anesthetic drugs, such as propofol, sevoflurane, have shown the ability of cardiac protection [6], but anesthetic drugs have not been widely used to prevent cardiovascular event. Meanwhile, many anesthetic drugs with cardiovascular protection are common adjuvant methods for the treatment of perioperative SVT [7].

Dexmedetomidine (Dex), a highly selective $\alpha$-2 receptors agonist, is used as sedative and anaesthetic adjuvants [8]. Many evidences suggested that Dex can serve as a potential treatment for arrhythmias. Dex can significantly affect the cardiac electrophysiology and conduction system, and thus depress sinus and atroventricular nodal function [9, 10]. Liu et al. [11] confirmed that Dex can reduce ventricular rate and improve atrial fibrillation in pediatric patient with cardiac surgery. Ji et al. [12] also found that Dex can be effective in reducing cardiovascular and cerebrovascular complications and mortality in patients
one year after cardiac surgery. Increasing evidence suggests that cardiovascular effect of Dex strongly supports the antiarrhythmic effects.

Previous studies of pediatric patients have shown that Dex can effectively terminate perioperative tachyarrhythmia, the therapeutic effect of Dex on SVT in adults, especially patients undergoing non-cardiac surgery, is unclear and should be explored [13–16].

**Methods**

The protocol of this study was approved by the medical ethics committee of hospital, and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT04284150), following the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement [17].

Adult patients with SVT undergoing elective non-cardiac surgery were eligible for the trial. Forty-six patients with SVT, aged between 35 and 61 years, American Association of Anesthesiologists (ASA) I and II, undergoing elective non-cardiac surgery were recruited for the study. Patients were excluded from the study in following cases, such as suffering from significant hemodynamic instability, having recent history of complete atrioventricular block, suffering from other types of arrhythmia, not SVT and coupling with anaphylaxis to α-2 receptors agonist or benzodiazepines.

**Diagnostic criteria for SVT**

SVT is defined as abnormal cardiac rhythms with heart rates exceeding 100 beats/min at rest, and electrophysiologic substrate originating above the Bundle of His [18, 19]. We followed that convention and chose regular SVT including sinus tachycardia, atrial flutter, atrioventricular nodal reentrant tachycardia, atrioventricular reciprocating tachycardia, atrial tachycardia in our study.

**SVT management**

The patients calmed down for 5–10 minutes after getting into the operating room. Forty-six patients were randomly divided into Dex group and midazolam group according to the randomisation schedule with intravenous infusion Dex (1.0 µg/kg, Jiangsu Hengrui Pharmaceutical Co., Ltd., Lianyungang, China) or midazolam (0.06 mg/kg, Jiangsu Nhwa Pharmaceutical Co., Ltd., Xuzhou, China) using a micro-pump for 10 minutes. In this study, using a double-blind method, Dex and midazolam were administered by an anesthesiologist, and the therapeutic effect was evaluated by a professional cardiologist. The patients were randomly allocated by sealed envelope technique done according to the randomisation schedule and patients, treating anaesthetist and assessors were all blinded as to group allocation. Only a nurse who prepared the medications for patients with SVT knew group allocation, but not involved in the study. SVT was terminated and converted to normal sinus rhythm (60–100 bpm), which was used to assess the therapeutic effect of Dex and midazolam. It is mandatory that stabilization and termination of the
arrythmia. Patients who did not respond to Dex and midazolam, were subsequently treated with the appropriate and conventional approach.

SVT occurred pre-anesthesia in patients in this study. The research group adopted the following points for all the study cases: (1) In this study, ECG, vital signs and hemodynamics were strictly monitored in all patients. (2) Patients with SVT pre-anesthesia and hemodynamic stability were selected. If SVT improved after treatment, they could continue elective surgery. (3) All patients in this study were evaluated by three senior clinicians (including one cardiologist and two anesthesiologists) before decision to undergo surgery or to postpone surgery.

**Patient monitoring**

The patients monitoring indicators, including therapeutic effects of SVT, heart rate (HR), mean arterial pressure (MAP), pulse oxygen saturation (SpO\textsubscript{2}), the Observer’s Assessment of Alertness/Sedation (OAA/S) score and heart rate variability (HRV) frequency-domain parameters including normalized low frequency power (LFnorm), normalized high frequency power (HFnorm), and the balance ratio of sympathetic to vagal tone (LFnorm/HFnorm) were recorded every 5 minutes, including T0 (5 minutes before the infusion), T1 (the first 5 minutes during the infusion), T2 (the second 5 minutes during the infusion), T3 (the first 5 minutes after the end of the infusion), and T4 (the second 5 minutes after the end of the infusion).

**HRV Monitoring System**

The HRV monitoring system (Healink Ltd., Bengbu, China) was used in this study, which can record and analyze HRV frequency-domain parameters including HF, LF, and LF/HF that are one of the noninvasive quantitative indicators of autonomic nerves regulation of cardiac activity. In frequency-domain analysis, LFnorm and HFnorm, which mainly reflect sympathetic activity and vagal activity, are the normalized values of LF and HF, respectively. LFnorm/HFnorm as balance ratio of sympathetic to vagal tension can more directly reflect the change of sympathetic and vagal regulation than a single LFnorm or HFnorm.

**Evaluation of sedation depth**

Sedation depth was assessed by the Observer's Assessment of Alertness/Sedation (OAA/S) score and documented as a score of 5 (responding readily to name spoken in normal tone); 4 (lethargic response to name spoken in normal tone); 3 (responding only after name is called loudly or repeatedly); 2 (responds only after mild prodding or shaking); 1 (no response to mild prodding or shaking); 0 (no respond to noxious stimuli) [20].

**Sample size calculation**

The sample size of this study was calculated based on a two-sided alpha error of 0.05, beta of 0.10 and power of 0.95. Because our previous works had demonstrated that Dex had a significant therapeutic effect for SVT, we estimated therapeutic efficiency at least 50% in patients with SVT treated with Dex.
After calculation, we deemed that at least 17 patients per group would be required. After considering a 10% drop out we decided to enrol forty-six patients in our trial to account for possible protocol deviation.

**Statistical analysis**

Statistical analysis were performed with IBM SPSS 25.0 (IBM Corp, Armonk, NY, USA). All analyses used two-sided significance tests. The data were expressed as median (inter-quartile range) or mean (standard deviation, SD) if not specified. Categorical variables are presented as n (%). The comparisons between two groups were done with independent sample t-test. Intra-group comparisons were performed using the analysis of variance test of repeatedly measured data. Frequency percentages were analyzed using $\chi^2$-test. A $P$-value < 0.05 was considered statistically significant.

**Results**

**Participant Characteristics**

There was no significant difference in the general information between Dex group and midazolam group ($P > 0.05$) (Table 1).

|                         | Dex group | Midazolam group | $P$ value |
|-------------------------|-----------|-----------------|-----------|
|                         | (n = 23)  | (n = 23)        |           |
| Male sex                | 11(47.8)  | 13(56.5)        | 0.609     |
| Age (year)              | 43.4 ± 5.6| 44.1 ± 4.9      | 0.559     |
| BMI (kg/m$^2$)          | 23.15 ± 3.73| 22.61 ± 2.55  | 0.771     |
| ASA                     |           |                 | 0.730     |
| I                       | 5(21.7)   | 6(26.1)         |           |
| II                      | 18(78.3)  | 17(73.9)        |           |
| Affiliated disease      |           |                 |           |
| Abnormal electrocardiogram before operation | 3(13.0) | 2(8.7) | 0.636 |
| Hypertension            | 2(8.7)    | 2(8.7)          | 1.000     |
| Diabetes                | 1(4.3)    | 2(8.7)          | 0.550     |
| Coronary heart disease  | 1(4.3)    | 0               | 0.312     |
| Hypokalemia             | 1(4.3)    | 0               | 0.312     |

All data were presented as percentage except age and BMI were presented as mean ± SD.
Primary outcome: the treatment efficiency of SVT

Among the twenty-three patients with SVT in Dex group, the effective rate were 13/23 (56.5%), 18/23 (78.3%), 18/23 (78.3%), 21/23 (91.3%) at T1, T2, T3 and T4, respectively. However, the effective rate of SVT was 2/23 (8.7%) at T1, T2, T3 and T4 in midazolam group, which was distinctly different from Dex group \(P< 0.001\). Figure 1 showed four patients with typical SVT converted to NRS during 4–18 minutes after infusion Dex. However, other antiarrhythmic treatments were considered as further treatment measures according to the treatment effect in the study.

Secondary outcome: the change of HRV

Compared to T0, LFnorm and LFnorm/HFnorm were decreased, and HFnorm were elevated, furthermore, the changes in HFnorm, LFnorm and LFnorm/HFnorm have statistical significance in Dex group from T1 to T4 \(P< 0.05\). Compared to midazolam group, the changes of HFnorm and LFnorm/HFnorm have statistical significance in Dex group \(P< 0.05\). However, the changes in HFnorm, LFnorm and LFnorm/HFnorm in midazolam group have no statistical significance \(P> 0.05\) (Fig. 2).

The vital signs

Compared to T0, HR and MAP in two groups were obviously decreased, and HR and MAP in Dex group were apparently lower than midazolam group from T1 to T4 \(P< 0.05\). There was no statistically significant difference for SpO\(_2\) from T0 to T4 in Dex group \(P> 0.05\). Compared with T0 or Dex group, SpO\(_2\) in midazolam group obviously decreased at T2 \(P< 0.05\) (Fig. 3).

The degree of sedative and adverse effects

Compared with T0, the OAA/S score decreased from 5.00 (0) to 3.76 (0.44, \(P< 0.001\)) and 3.07 (0.78, \(P< 0.001\)) in Dex group and midazolam group, and the OAA/S score in midazolam group was lower than Dex group at T4 \(P< 0.05\). Compared with T0, the OAA/S score in two groups was obviously decreased at T4, and the OAA/S score in midazolam group was lower than Dex group at T4 \(P< 0.05\).

Three patients developed mild hypotension that responded well to intravascular volume in Dex group. Three patients in midazolam group developed a decrease of SpO\(_2\) (below 90%), which was improved by mask oxygen inhalation. None of patients developed clinically significant bradycardia, hypotension, and anoxia. None of patients in this study developed clinically significant cardiovascular risk events during the post-operative period in hospital.

Discussion

The primary result of this study was that perioperative use of Dex had a significant therapeutic effect for SVT in adult patients and the adjusting effect of Dex on the function of cardiac autonomic nervous might be one of the antiarrhythmic mechanisms of action of Dex.
Perioperative use of Dex in pediatric patients undergoing cardiothoracic operations can decrease incidence of ventricular and supraventricular tachyarrhythmias [21], suggesting that its antiarrhythmic effect in adult patients undergoing non-cardiac surgery needs to be further explored. Our results had demonstrated that Dex had an effective therapeutic effect and few adverse effects for the treatment of patients with SVT, who simultaneously suffered from hypokalemia, and/or diabetes, and/or hypertension, and/or coronary heart disease. Thirteen patients with SVT were remarkably improved only 5 minutes after infusion of Dex (1.0 µg/kg), and SVT of twenty-one patients without recurrence of SVT in Dex group were eventually controlled and returned to NSR by continuous intravenous infusion of Dex for 10 minutes. These evidences demonstrated that Dex had therapeutic effects on SVT patients coupling with different diseases.

The HRV results had shown that HFnorm was elevated, while LFnorm and LFnorm/HFnorm were decreased after twenty-three patients infused Dex in Dex group, which revealed that Dex changed the balance between the sympathetic and parasympathetic tone, and regulated cardiac autonomic nervous system, and powerfully enhanced vagal neural activity, thereby, overall rhythm or heart rate control was achieved. These data suggested that Dex may mainly reduce sympathetic tension to decrease the ability of inducing the arrhythmia.

There are many types of SVT, which are associated with disorders of autonomic nervous regulation of cardiac activity, reentrant excitation and enhancement of autorhythmicity. Some studies have shown that paroxysmal SVT have an imbalance of autonomic nervous system, for example, injury to cardiac parasympathetic nerves, which can result in predominance of sympathetic activity during thoracic surgery that is the primary autonomic mechanism triggering postoperative SVT, thus, tachyarrhythmia is treated by stimulating the vagus nerve and regulating the activity of autonomic nerve [22, 23]. Using the clinical recommended dosage, Dex can act on the medullary vasomotor center leading to decrease of catecholamine released from the nerve terminal [24], which results in bradycardia and the negative chronotropic effects of the heart (e.g. treat tachyarrhythmia) [25]. Dex containing an imidazole ring can activate imidazoline receptors in the central nervous system, which can prevent adrenaline-induced ventricular tachycardia [26]. It is reported that Dex had therapeutic effect on atrial and junctional tachyarrhythmias [27], and can significantly decrease heart rate via regulating autonomic nerve homeostasis [28]. Kamibayashi T et al. [28] by animal-dogs study demonstrated that the antiarrhythmic effects of Dex are mediated through enhancement of the vagal neural activity. In our study, we also demonstrate that Dex treats SVT related to changing the function of cardiac autonomic nervous system. In a word, Dex with multiple administrations is appropriate and effective for treating SVT, and may be an ideal agent for SVT.

Few patients developed clinical bradycardia, hypotension, respiratory depression, hyoxemia and hemodynamic disorder in Dex group during infusion of Dex, which is perhaps due to using Dex alone, and thus a synergistic or additive effect with other sedative and analgesic drugs is impossible. Furthermore, Dex simultaneously maintains a sufficient level of sedation with a unique property of easy arousal. Although Dex causes mild hypotension, because of its unique minimal effect on respiration compared
with most other sedative drugs, Dex is widely used in clinical practice. In addition, Dex does not cause any significant sinus pause or asystole. It has no negative inotropic effector proarrhythmic effect, in contrast with many other agents such as β-adrenergic antagonists and amiodarone. Moreover, Dex has bronchodilatory properties, therefore, it can still be used during asthma attacks.

SVT is associated with adverse stimulus such as emotional tension and anxiety, cardiovascular risk factors and hypoxia. Emotional tension and anxiety are the most common cause of perioperative SVT. It is also worth considering that sedation treatment should be taken in patients with SVT pre-anesthesia. Therefore, midazolam as a sedative was selected as the control group to compare the therapeutic effect of Dex on SVT in this study. Although the sedation degree in midazolam group was deeper than Dex group, only two patients are eventually improved, and other patients failed to respond in midazolam group. Earlier studies have shown that intravenous infusion of midazolam 5.0 mg did not alter the reentrant tachycardia [29]. These data indicated that the sedation may not be the mechanism of Dex for the treatment of SVT.

Dex may be used during general anaesthesia as an adjuvant [30]. General anesthesia comprises of unconsciousness, analgesia, anti-stress, and immobility along with maintenance of physiological stability [31]. Dex, which combines sedative, anti-stress and enhancing analgesic effects, may be more applicable than other antiarrhythmic drugs to treat SVT in patients received general anesthesia.

Limitations

It is reported that large doses or rapid infusion of Dex can potentially have an adverse impact on patients with underlying heart disease, which may cause left ventricular dysfunction and hemodynamic instability [32]. Flores-González et al. [33] reported that cessation of Dex for 12 hours after continuously infusing it for 10 days resulted in occurrence of paroxysmal SVT for a 4-years-old girl. However, our observation period was the time when patients was in the operating room, and we might have missed arrhythmias that occurred afterwards. Moreover, it was impressive with a significant (91.3%) termination of SVT using Dex, which may be associated with chosen types of SVT. Therefore, there are more clinical research needed to explore the treatment efficiency of various types of SVT using Dex. Further clinical study is also needed to clarify the mechanism of effects, feasibility of wide clinical application, the dosage and rate of Dex for the treatment of SVT. Notably, this was a prospective and randomised study that confirmed the mechanism and effectiveness of Dex in the treatment of SVT. The conclusion of this study can provide a new therapeutic regimen for treating SVT using Dex.

Conclusions

Dex may be highly effective treatment choices for terminating SVT, which may be correlated with altering of cardiac autonomic nervous function by Dex. Dex is a promising agent for SVT in the future, especially patients undergoing general anesthesia or sedation.
Abbreviations

ASA: American Association of Anesthesiologists; BMI: Body mass index; Dex: Dexmedetomidine; HFnorm: normalized high frequency power; HR: Heart Rate; HRV: Heart Rate Variability; LFnorm: normalized low frequency power; LFnorm/HFnorm: balance ratio of sympathetic to vagal tension; MAP: Marterial Pressure; NSR: Normal Sinus Rhythm; OAA/S: the Observer's Assessment of Alertness/Sedation; SpO2: Pulse Oxygen Saturation; SVT: Supraventricular Tachycardia

Declarations

Ethics approval and consent to participate

This study was approved by the institutional ethics committee of the affiliated Lianyungang No. 2 people’s hospital of Bengbu Medical College registry number: 2020K002 on January 14, 2020 and the protocol was registered at ClinicalTrials.gov registry number: NCT04284150 on February 13, 2020. All patients participating in this trial signed informed consent.

Consent for publication

Not applicable.

Availability of data and material

The data sets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors’ contributions

Study concept: JLZ

Study design: CWH, XY, XG

Study conduct: CWH

Analyzed data: CWH, SNY, QZ

Drafted manuscript: CWH, YX, JLZ
Recruited patients: XG, SNY, QZ

Revised manuscript: JLZ, YX

All authors read and approved the final manuscript.

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