DEXMEDETOMIDINE FOR PREVENTION OF SUPRAVENTRICULAR TACHYDYSRHYTHMIAS AFTER NON CARDIAC THORACIC SURGERY

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Abstract:

Background*: This study was done to evaluate the efficacy of dexmedetomidine (DEX) in prevention of supraventricular tachyarrhythmias (SVTs) after non cardiac Thoracic Surgery.* ***Methods:*** *Sixty five patients were enrolled in our study scheduled for elective non cardiac thoracic surgery. The patients were randomly assigned into two groups: Control Group 33 patients who did not receive dexmedetomidine prophylaxis and dexmedetomidine Group enrolling 32 patients who will receive continuous infusion of dexmedetomidine 0.2 µg/Kg/h which was initiated with induction of anesthesia and continued for 24h. Patients were observed throughout the first three days in ICU for the incidence of supraventricular dysrhythmias.* ***Results****: There were no significant differences between dexmedetomidine and control groups in patient characteristics & surgical Data. Eleven patients (36.7%) in group C developed (SVTs) of which eight had atrial fibrillation and three developed supraventricular tachycardia. In group D the incidence of SVTs was 10% (three patients) which was significantly less (p =0.031) when compared to matched control group as two patients in group D developed supraventricular tachycardia and one patient had AF. Patients in group C received significantly more PCA morphine and ketorelac than group D to achieve the same quality of analgesia. The mean time of ICU stay was significantly longer in group C (86 ±11hrs) versus (74±15 hrs) in group D (p =0.001), but there was no significant difference between the two groups in the incidence of adverse effects.* ***Conclusions:*** *We conclude that dexmedetomidine infusion can safely reduce the incidence of (SVTs) after non-cardiac thoracic surgery.*

Key words: dexmedetomidine, supraventricular tachydythrysmias, morphine, non-cardiac thoracic surgery.

Introduction:

Cardiac dysrhythmias are an important cause of morbidity and mortality in the perioperative period [(1)]. They are more common after major thoracic surgery and most often supraventricular in origin [(2)], of which the atrial fibrillation is the commonest [(3)]. The peak of onset of atrial arrhythmia is 2–3 days after thoracic surgery with up to 85% of these episodes converting to sinus rhythm with rate or rhythm control management during hospitalization [(4)]. The onset time of atrial arrhythmias and postoperative myocardial ischemia are similar and most probably due to autonomic nervous system imbalance [(5)]. The incidence of atrial

fibrillation is between 12.5 and 33% [6] after an anatomical resection as lobectomy, bi-lobectomy, pneumo-nectomy or esophagogastrectomy, most likely related to the effect of surgical trauma to the atria and to sympathovagal fibers supplying the sinus node. Autonomic neural fibers injury may lead to sensitization of the atrial myocardium to the circulating catecholamines (denervation super-sensitivity) [7]. Vagal withdrawal and/or adrenergic hyperactivity may promote these arrhythmias in the early postoperative period [8].

Many drugs have been used to ameliorate the incidence of postoperative arrhythmias to improve clinical outcomes and shorten hospital stay after thoracotomy as digoxin, β-blockers, calcium channel blockers, amiodarone, magnesium, statins and partial sympathectomy with epidural analgesia, with variable efficacies [9], but the actual causes and prophylaxis of (SVTs) remain unclear [3]. Dexmedetomidine (DEX) is a potent highly selective alpha-2 receptors agonist having multifaceted attributes of analgesia, and sedation with sympatholytic, and anxiolytic effects that blunt many of the cardiovascular responses in the perioperative period. Its trade name is Precedex. It reduces the sedative and analgesic requirements without causing respiratory depression due to its unique mechanism of action as an agonist of alpha-2 receptors in certain parts of the brain [10]. Dexmedetomidine is the S-enantiomer of medetomidine [11].

Methods:

After approval of National Cancer Institute Ethics Committee and obtaining informed written consent from each patient before operation, this prospective randomized controlled study was started. Sixty five patients were enrolled in our study. All patients had a primary or metastatic lung cancer, or esophageal cancer that required elective thoracic surgery. The patients were randomly assigned into two groups:

1- The Control Group (Group C): 33 patients who will not receive dexmedetomidine prophylaxis.
2- Dexmedetomidine Group (Group D): enrolling 32 patients who will receive continuous infusion of dexmedetomidine.

Exclusion Criteria:

Patients with one or more of the following were excluded from the study.

1- Patients with a history of preoperative chronic supraventricular tachyarrhythmias. All patients had sinus rhythm preoperatively.
2- Patients receiving digoxin, ß-adrenergic blockers or calcium-channel blockers.
3- Patients with poor cardiac function; preoperative transthoracic echocardiograms were performed & patients with ejection fraction less than 50% were excluded.
4- Patients with previous adverse reaction or contraindication to any of the used medications.

Patients randomized in Group D had a continuous infusion of dexmedetomidine 0.2 µg/Kg/h which was initiated with induction of anesthesia and continued for a total duration of 24h in intensive care unit (ICU).

All patients received premedication with bromazepam (calmepam, 1mg) the night before surgery and an intramuscular injection of 1mg of atropine and 5-10 mg of morphine one hour before surgery. A standardized general anesthetic technique was used, consisting of propofol (1.0 to 2.0 mg/kg) and cisatracurium (0.1 to 0.15 mg/kg) for induction. Isoflurane in oxygen, cisatracurium and fentanyl boluses as needed were used for the

maintenance of anesthesia. All patients required one lung ventilation.

Surgery was performed by experienced oncology surgeons using standard thoracotomy incision. After recovery from anesthesia all patients enrolled in the study were admitted to surgical ICU. Patient control analgesia (PCA) was started to all patients immediately on admission to the ICU. The PCA reservoir bag (Accufuser selectus ®. Made in Korea) of 200ml capacity contained 100 mg of morphine in normal saline (½ mg/ml) and 150 mg ketorolac (¾ mg/ml). The setting for PCA was 2 ml/h background infusion, 1 ml bolus with a 15 min lockout interval continued throughout the entire observation period if needed. Inadequate analgesia in both groups was treated with 3mg of morphine IV once daily. Our goal was to ensure adequate analgesia with Verbal Analogue Score (VAS) less than 4/10.

Patients were continuously monitored for hemodynamic variables including arterial blood pressure, heart rate, and central venous pressure, SaO2, EtCO2, both intraoperative and as long as the patient stayed in ICU. Daily arterial blood gases, complete blood picture, serum electrolyte and chest radiographs were obtained. In addition, a 12-lead electrocardiogram was obtained every 24hrs and if there was any attack of dythrythmia.

Patients were evaluated throughout the day by an anesthesiologist in the ICU for any side effects or complications; as shortness of breath, hemodynamic changes, pruritus, nausea and vomiting, and mental changes. The endpoint was significant supraventricular tachyarrhythmias with heart rate of 120 bpm or more other than sinus tachycardia occurring for more than 30 seconds requiring treatment due to a rapid ventricular rate, hemodynamic compromise or symptoms such as shortness of breath and fatigue. The onset time and duration of each attack, and the maximum HR during the attack were recorded.

Supraventricular tachycardia was treated with propranolol 1mg infusion repeated according to the response. Atrial fibrillation with rapid ventricular response were treated with amiodarone 300 mg loading dose via central vein catheter over an hour and followed by 900 mg infusion over 24 hrs. AF with hemodynamic compromise was managed with synchronized cardioversion. For symptomatic bradycardia (heart rate, < 50 bpm) with systolic hypotension < 90 mm Hg) dexmedetomidine was discontinued temporarily till the heart rate was controlled and intravenous atropine 1mg IV was given and repeated to a maximum of 3mg. All the heart beats in the ICU were continuously monitored with an electrocardiogram (ECG) monitor (Component Monitoring System; General Electric) and recorded until the morning of the third postoperative day. Daily morphine and ketorolac consumption, and length of stay in ICU were recorded. The quality of analgesia was assessed using a 10 cm VAS score, where zero denotes no pain and 10 the worst pain.

Statistical Analysis:

Data were collected, and tabulated and then analyzed using SPSS® version 16.0. Numerical data were presented as mean and standard deviation while categorical data were presented as frequency and percentage. Statistical analysis was performed using Student “t” test and Fisher Exact test for comparison between the two groups, any difference with $p < 0.05$ was considered statistically significant.

Results:

From September 2008 to January 2011 a total of 65 patients were enrolled in this randomized controlled study. Three patients in Dexmedetomedine (group D) and two patients in Control group were excluded because of unexpected surgical complications. One patient developed surgical emphysema complicated by pneumo-pericardium and ECG changes, the other four patients developed extensive bleeding and required inotropic support (adrenaline infusion) which might bias our results. Sixty patients completed the study, 30 in each group. Patient characteristics and surgical data are presented in (Table 1). The two groups were similar with respect to age, sex, weight and height, ASA physical status, preoperative pulmonary function tests (FEV1, FVC and PaO2), preoperative chemotherapy, type of surgery, operative time and blood loss (table1).

Table 1: Patient Chrachteristics & Surgical Data

	Group C (30)	group D (30)	*P* value
Age(yr)	49±14	47±12	0.555
Sex (M/F)	21/9	19/11	0.785
Height (cm)	159± 17	163± 15	0.096
Weight (kg)	69± 15	65± 17	0.338
ASA physical status II/III	23/7	21/9	0.771
Preoperative FEV1, % predicted	64± 14	67 ±13	0.393
FVC, % predicted	85±10	89± 16	0.250
Preoperative PaO_2 (mm Hg)	93.2± 6.4	91 ± 5.9	0.162
Chemotherapy Medication (yes/no)	20/10	24/6	0.382
Operative time (min)	269±36	278±39	0.357
Type of Surgery (n)			
Metastatectomy	4	5	1.000
Lobectomy	10	8	0.779
Pneumonectomy	6	4	0.731
Pleuropneumonectomy	3	4	1.000
Oesophagectomy	7	9	0.771
Blood Loss (ml)	710±450	834±325	0.226

Values are expressed as mean ± standard deviation.

Fourteen patients enrolled in our study developed (SVTs) in the first three days after thoracotomy, nine of them had AF. Most of these SVTs, 92.9% were converted to sinus rhythm with rate- or rhythm-control medication in ICU except one patient (7.1%) in (group C) discharged from ICU with rate controlled AF.

Table 2: Types of SVTs developed during the observational period

	group C	group D	*P* value
Supraventricular tachycardia (n)	3	2	
Atrial fibrillation (n)	8	1	
Total (n)	11 (36.7%)	3 (10%)	0.031

n = Number of patients who developed the defined arrythmia.

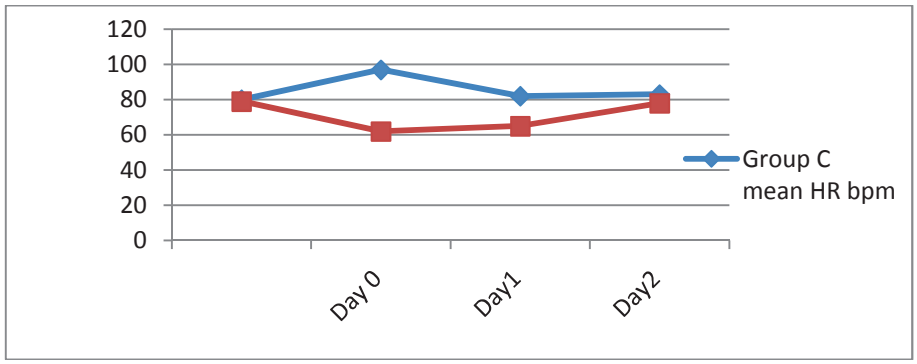

FIG 1: Heart Rate Changes during observation period.

Eleven patients (36.7%) in group C developed SVTs of which eight had Atrial Fibrillation and three developed supraventricular tachycardia. In group D the incidence of SVTs was 10% (three patients) which was significantly less when compared to matched control group. Two patients in group D developed supraventricular tachycardia and one patient had AF (table 2). Atrial fibrillation was the predominant dysrhythmia in our 14 patients (64.2%) which responded to amiodarone therapy and converted to sinus rhythm in most of patients. Supraventricular tachycardia was treated with propranolol 1mg infusion repeated according to the response.

Table 3: Duration, Onset time and mean Heart rate of SVTs' episodes

	GroupC	GroupD	
Mean duration of SVTs' episodes (hrs)	9.1±3	8.5±6	0.626
Mean maximum heart rate during each episodes (bpm)	153±20	141±15	0.018
Mean time for onset of each episodes after surgery (hrs)	27.1±14.5	49±9.7	0.001

Values are expressed as mean ± standard deviation.

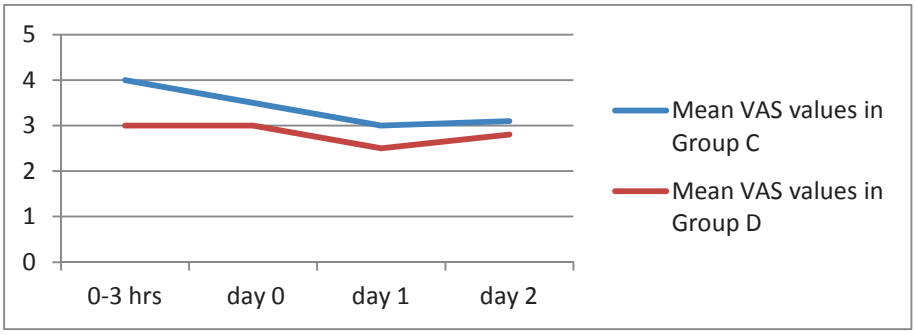

FIG 2: Mean VAS values in immediate postoperative period and rest of day 0, day1 and day2 (insignificant difference between two groups).

The mean duration of SVTs attacks of each patient was 8.5±6 hrs in group D compared to 9.1±3 hrs in group C, this was not statistically significant (p = 0.626). The mean maximum heart rate recorded during the attack in group D was 141 ± 18 bpm versus 153 ± 20 bpm in group C with which was statistically significant (p = 0.018) but clinically insignificant. The mean time for the onset of SVTs after surgery was significantly longer in group D patients 49 ±9.7 hrs than in group C patients 27.1 ± 14.5 hrs (p = 0.001) (table 3). Compared with Control group, group D patients had slower mean 24-h heart rate at day 0 and day1 after operation, (***p*** value=0.001), Furthermore, group D patients developed a significant decrease in mean HR below preoperative baseline at postoperative day 0 and day one (***p*** value: 0.001) but there was no significant differences of preoperative and postoperative values in day 2. On the contrary in the control group there were significant postoperative rise in heart rate above preoperative values in day 0 but there were no significant differences of preoperative and postoperative values in day1 and day 2 (figure 1).

Two patients in (group D) and one in (group C) had a sinus bradycardia below 60 during observation period without hemodynamic changes that didn't necessitate any intervention, only one patient in (group D) had symptomatic bradyhcardia 45 bpm with hypotention who required atropine 1mg IV and DEX infusion was stopped for 2.5 hours till the heart rate was controlled.

Table 4: Mean Analgesic Consumption during the observation period.

	Group C	Group D	*P* value
Morphine requirements in 72 hrs (mg)	97.8±18	61.7 ± 21	0.001
Ketorelac requirements in 72 hrs (mg)	121±21	71±30	0.001

Values are expressed as mean ± standard deviation.

Moreover, patients in group C received significantly more PCA Morphine and Ketorelac than group D during the observation period to reach the same quality of analgesia (table 4) as there were no significant difference between two groups in mean VAS values during observation period (figure 2).

Table 5: Incidence of side effect during observational period

	group C	group D	*P* value
Bradycardia (n)	1	4	0.353
Pruritus (n)	9	3	0.104
Nausea and vomiting (n)	12	5	0.084

(n) total number of patients who developed episodes of side effects.

There were no significant differences in incidence of postoperative side effect between the two groups during observational period (table 5). The mean time of ICU stay was significantly longer in group C (86 ±11hrs) versus (74±15 hrs) in group D (*p* =0.001) (figure 3).

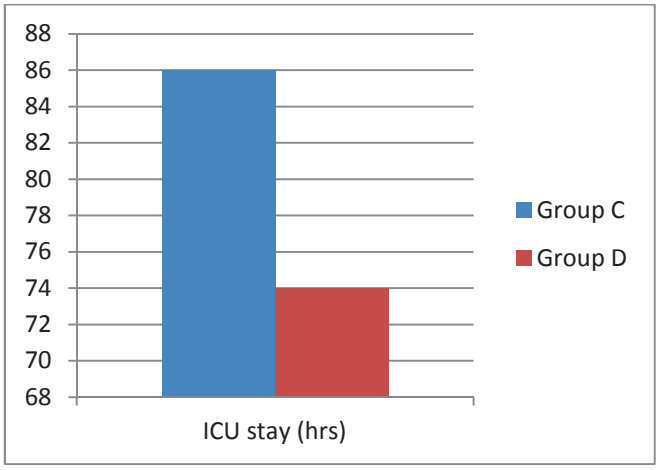

FIG 3: Surgical ICU stay

Discussion:

The main goal of our study - that differed from previously published data about dexmedetomidine - was to find out whether dexmedetomidine infusion will prevent or at least decrease incidence of post operative SVTs after major non-cardiac thoracic surgeries. Dexmedetomidine is a highly selective alpha 'sub 2' adrenoreceptor agonist. It has anxiolytic, sympatholytic and analgesic effects. It can be used for up to 24 hours in post-surgical patients [12-15]. Previous studies suggested that predominance of sympathetic activity due to injury of cardiac parasympathetic nerve after thoracic surgery is the primary autonomic mechanism triggering postoperative SVTs. They suggested that modulation of sympathetic and/or parasympathetic nervous systems may be effective in preventing postoperative SVTs [16]. This was supported by Oka et al, 2001 study where partial sympathectomy with epidural local anesthetic administration reduced the incidence of AF after thoracic surgery [17]. Cardinale et al, 2007 found that enhanced adrenergic activity in the perioperative period is probably responsible for AF after thoracic surgery for lung cancer [18]. Extensive surgical stress, and increased sympathetic activity and hypoxemia are all proposed as possible mechanisms of SVTs after thoracotomy [19-21].

In our study we found that the incidence of post operative SVTs was significantly less in patients who received continuous infusion of DEX for 24h started with induction of anesthesia as compared with those who didn't receive DEX infusion (10% versus 36.7% respectively). Eight patients in group C developed Atrial Fibrillation (26.7%) and 3 patients developed Supraventricular Tachycardia (10%). While in group D two patients had an episode of Supraventricular Tachycardia (6.7%) and one had an episode Atrial Fibrillation (3.3%). This also reflected to the mean time of ICU stay which was significantly less in group D.According to the proposed mechanisms of genesis of SVTs in the postoperative setting, the decreased incidence of SVTs in group D in our study might be due to attenuation of the stress and adrenergic responses to surgery as a result of the highly selective alpha"sub 2" adrenoreceptor agonist activity of dexmeditomedine with its sympatholytic, sedative, and analgesic properties. Increased quality of analgesia by DEX infusion is very clear as there was a significant decrease in morphine and ketorelac consumption in dexmeditomedine group in our study. Reduced post-operative opioid requirements, thereby decreased the incidence of post-operative respiratory depression as well as other opioid side effects that may develop when morphine is given alone to achieve the same level of analgesia. Again hypoxemia and hypercapnia secondary to respiratory depression do contribute to genesis of SVTs.

Too many researchers studied incidence of postoperative SVTs in thoracic non-cardiac surgeries. They found that incidence of AF was ranging between 12.5% and 33% after lobectomy, bilobectomy, or pneumonectomy [2, 4, 5, 7, 22-28]. The incidence of AF/supraventricular tachycardia after esophago-gastrectomy was reported to be 17% and ranges between 13% and 25%. Some authors have made an association between increased mortality and AF following esophago-gastrectomy, but others have not [29, 30]. These results were concordant with ours as regards the incidence of postoperative SVTs in group C patients.

Previous studies showed that the peak onset time of SVTs was 2 to 3 days after surgery (31, 32). Accordingly we observed our patients for incidence of SVTs during the first three days in ICU. The onset time of SVTs was more delayed in group D when compared with group C. That is to say patients who developed SVTs in group D, the episode started after discontinuation of DEX infusion. But it is not recommended to use DEX infusions more than 24 hrs. Most of patients who had SVTs (92.9%) were converted to normal rhythm with rate- or rhythm-control medication in the ICU.

Conclusion:

We conclude that dexmedetomidine infusion can safely reduce the incidence supraventricular tachydythrysmias after major non-cardiac thoracic surgery.

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