Evaluation of effects of intravenous dexmedetomidine on analgesic and anesthetic requirement in thoracic surgeries with one lung ventilation: A prospective randomized study

Ajaiz Rasool¹, Raja Suhail Shounthoo², Aabid Hussain Mir³, Sheikh Irshad Ahmad⁴

Department of Anesthesiology SKIMS

ABSTRACT

Background: Dexmedetomidine has been shown to reduce the intraoperative requirement of anesthetic and analgesic agents.

Objectives: To evaluate the effects of intraoperative dexmedetomidine infusion in reduction of analgesic and inhalational anesthetic requirement in thoracic surgeries using one lung ventilation.

Material and Methods: This prospective randomized study was conducted in department of Anesthesiology and Critical Care of a tertiary care hospital. Sixty patients of American Society of Anesthesiologists (ASA) physical status I and II were randomly assigned to two groups, group 1 (n=30) received a loading dose of dexmedetomidine $0.3\mu\text{g.kg}^{-1}$ intravenously during induction of anesthesia, followed by a continuous infusion at a rate of $0.3\mu\text{g.kg}^{-1}.\text{hr}^{-1}$ continued up to two hours of the surgery and group 2 (n=30) received a volume matched bolus and infusion of saline (0.9% saline). For each case heart rate, peripheral oxygen saturation and mean arterial pressure were recorded intraoperatively at regular intervals. Total fentanyl consumption and isoflurane requirement were noted intraoperatively for both the groups keeping bispectral index (BIS) 40-60.

Results: The groups were similar with respect to baseline characteristics and distribution of study subjects. The mean fentanyl consumption and the volatile agent requirement to achieve a particular intraoperative BIS value were significantly higher in group 2 compared to group 1 (p 0.002 and p 0.001 respectively).

Conclusion: Dexmedetomidine infusion provides effective intraoperative analgesia and reduces the isoflurane requirement to achieve a particular depth of anesthesia during thoracic surgeries performed using one lung ventilation.

Key words: Dexmedetomidine, One lung ventilation, Thoracic surgeries, Analgesia, Anesthesia

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INTRODUCTION

The technique of one-lung ventilation improves exposure of intrathoracic structures, thereby providing optimal surgical conditions, since adequate pulmonary exposure facilitates resection and reduces surgical time.^{1,2} However, all these surgical procedures involve thoracotomies and extensive tissue handling, with accompanying requirement for effective perioperative analgesia.

Dexmedetomidine is an α_2 receptor agonist and has been approved for analgesia and sedation in humans. These α_2 receptors are present on dorsal horns of spinal cord and are involved in release of endogenous opioids. Thus, the α_2 -

adrenoceptor agonists may offer interesting new possibilities in the treatment of pain and may help to reduce intraoperative opioid requirements, as clonidine does.^{3,4,5}

Dexmedetomidine is found to have sedative, analgesic, hypnotic, anxiolytic and properties of sympatholysis. Dexmedetomidine has been shown to reduce the requirements of inducing agents, such as thiopentone.⁶

Correspondence:

Dr. Aabid Hussain Mir, MD
Department of Anesthesiology SKIMS
Email: meeraabid111@gmail.com

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Several studies have shown a substantial reduction in the maintenance concentrations of isoflurane in patients treated with either low or high doses of dexmedetomidine and isoflurane without premedication.^{7,8}

The present study was undertaken to observe the effect of dexmedetomidine on anaesthetic and analgesic requirements during thoracotomies using One Lung Ventilation in adults.

MATERIAL AND METHODS

This prospective randomized study was conducted in Department of Anesthesiology and Critical Care Sheri Kashmir institute of medical sciences Srinagar over a period of one and a half years from December 2013 to June 2015 after approval from the departmental review board and written informed consent from the patients. 60 patients of ASA physical status I and II in age group 18-65 years undergoing thoracic surgeries using one lung ventilation (OLV) were randomly divided by a computer generated randomization list into two groups of 30 patients each. **Group 1** received dexmedetomidine prepared as a $4 \mu\text{g.mL}^{-1}$ solution in a total volume of 50 mL as a bolus of 0.075 mL.kg^{-1} ($0.3 \mu\text{g.kg}^{-1}$ of dexmedetomidine) intravenously. After completion of the bolus dose, a continuous infusion of dexmedetomidine was started at $0.075 \text{ mL.kg}^{-1}.\text{h}^{-1}$ ($0.3 \mu\text{g.kg}^{-1}.\text{h}^{-1}$ of dexmedetomidine) and continued up to two hours of the operative procedure and **Group 2** received normal saline in a similar volume as group 1. The study cases included patients with unilateral lung mass and unilateral lung hydatid disease. Patient with known conduction disturbances, severe valvular disease or coronary artery disease, patients taking ACE inhibitors and/or clonidine, those with severe chronic obstructive pulmonary disease (COPD) and with deranged pulmonary function tests, patients with autonomic neuropathy, or those diagnosed with intracranial space occupying lesions (ICSOL) were excluded from the study.

No premedication was used in any of the patients, standard ASA monitoring was used (ECG, pulse oximetry, end tidal carbon dioxide, blood pressure and temperature). Anaesthesia was induced using propofol (2.5 mg.kg^{-1}), fentanyl ($2 \mu\text{g.kg}^{-1}$) and atracurium (0.6 mg.kg^{-1}), and an appropriate size PVC double lumen endotracheal tube was used to secure the airway and to provide lung isolation, radial artery cannulation was done for invasive blood pressure monitoring and sampling. Anaesthesia was

maintained during the operation using oxygen in nitrous oxide with inhaled isoflurane titrated to bispectral index (BIS) value of 40-60; FiO_2 was adjusted to maintain oxygen saturation (SPO_2) $> 90\%$. Atracurium in dose of 0.1 mg.kg^{-1} in boluses was used for maintaining muscle relaxation. An arterial blood gas sample was obtained during two lung ventilation prior to starting one lung ventilation. Second blood gas was obtained 10 minutes after the institution of OLV. After obtaining the second arterial sample a bolus of 0.075 mL.kg^{-1} of the solution ($0.3 \mu\text{g.kg}^{-1}$ of dexmedetomidine or normal saline) was administered intravenously. After completion of the bolus dose, a continuous infusion of dexmedetomidine or normal saline was started at $0.075 \text{ mL.kg}^{-1}.\text{h}^{-1}$ and was continued up to two hours of surgery. A third arterial sample was obtained 15 minutes after dexmedetomidine/normal saline bolus.

Intraoperative hypotension (defined as a fall in mean arterial pressure of more than 20% of baseline or a systolic blood pressure of less than 90 mmHg), was managed using boluses of phenylephrine ($50 \mu\text{g}$), however the patients who developed bradycardia along with fall of blood pressure were excluded from the study. Supplemental fentanyl was given to patients getting intraoperative tachycardia &/or hypertension.

Intraoperatively various parameters were evaluated including, differences in hemodynamic parameters and total consumption of phenylephrine. Primary outcome of the study was intraoperative fentanyl consumption and the intraoperative requirements of isoflurane for maintenance of BIS in range of 40-60.

Statistical analysis

Intraoperatively data was collected and summarized and then it was entered into a spreadsheet (Microsoft Excel) and then exported to Statistical software SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA). All the continuous variables were represented by descriptive statistics and the categorical variables were represented in terms of frequency and percentage. Data was analyzed by means of Chi-square test, Student's independent t-test and repeated measurement analysis. Data was presented by means of Bar and Line diagrams. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The demographic characteristics and the distribution of subjects were comparable in two groups and were

statistically insignificant (Table 1).

Table 1: Demographic characteristics of the study groups

Parameter	Group 1	Group 2	p-value
Age (years)	51.2±7.47	49.3±7.06	0.307
Gender (M/F)	17/13	16/14	0.795
Weight (kg)	70.5±7.65	71.9±8.16	0.516

Values presented as mean ±SD

The baseline heart rate and that taken at intervals of 5 min, 10 min and 15 min was comparable between the two groups (p-value>0.05), whereas, the heart rate recorded at 30 min, 60 min, 90 min and 120 min was significantly higher in group 2 compared to group 1 with p value of <0.001 (Figure 1). The baseline mean arterial pressure and at intervals of 5 min, 10 min and 15 min was comparable between the two groups (p value>0.05), however, the mean arterial pressure recorded at 30 min, 60 min, 90 min and 120 min was higher in group 2 than in group 1 with p value of <0.001 (Figure 2).

Figure 1: Comparison of mean heart rate between the two groups

Fig. 2: Comparison of mean arterial pressure between the groups

The mean fentanyl consumption was significantly less in group 1 than in group 2 [group 1: 2.60±0.54 µg.kg⁻¹ & group 2: 3.05±0.56 µg.kg⁻¹ (p value 0.002)], indicating a better intraoperative analgesia in dexmedetomidine group (Table 2). The mean end tidal isoflurane was higher in group 2 as compared to group 1 [group 1: 1.03±0.051% & group 2: 1.29±0.124% (p<0.001)] (Table 3). Similarly, the average BIS value in group 1 was significantly lower than in group 2 [group 1: 42.31±1.02 & group 2: 43.41±1.96 (p=0.008)], indicating a greater volatile agent requirement in group 2 to achieve a particular intraoperative BIS value (Table 4).

Table 2: Total Intra-operative Fentanyl Consumption (µg.kg⁻¹)

Group	Mean	SD	P-value	Remarks
Group 1	2.60	0.54	0.002	Statistically Significant
Group 2	3.05	0.56		

Table 3: Comparison of end tidal isoflurane between the two groups

Comparison of End tidal isoflurane between two groups at various time intervals						
Time	Group 1 (N=30)		Group 2 (N=30)		P-value	Remarks
	Mean	SD	Mean	SD		
5 Min	1.51	0.170	1.51	0.187	0.886	Non-significant
10 Min	1.32	0.130	1.36	0.161	0.255	Non-significant
15 Min	1.23	0.162	1.28	0.146	0.160	Non-significant
30 Min	0.86	0.159	1.25	0.146	<0.001	Significant
60 Min	0.79	0.181	1.21	0.145	<0.001	Significant
90 Min	0.76	0.165	1.19	0.158	<0.001	Significant
120 Min	0.73	0.109	1.20	0.163	<0.001	Significant
Overall	1.03	0.051	1.29	0.124	<0.001	Significant

p-value<0.05-significant

Table 4: Comparison of BIS between the two groups

Comparison of BIS between two groups at various time intervals					
Time	Group 1 (N=30)		Group 2 (N=30)		P-value
	Mean	SD	Mean	SD	
5 Min	45.40	2.47	44.63	2.74	0.259
10 Min	44.50	2.06	44.40	2.31	0.860
15 Min	44.20	1.83	44.53	2.06	0.510
30 Min	39.17	1.98	43.77	5.30	<0.001
60 Min	41.13	2.08	42.87	3.23	0.017
90 Min	40.13	1.74	41.50	3.15	0.042
120 Min	40.90	1.67	42.17	2.56	0.027
Overall	42.31	1.02	43.41	1.96	0.008

BIS- Bispectral index, p-value<0.05-significant

DISCUSSION

One lung ventilation has emerged as a very effective method for thoracic procedures as it greatly improves the surgical exposure. But despite its various advantages, it greatly impairs the patient's physiology and may lead to various complications intraoperatively. The principal complications that arise from one lung ventilation are hypoxemia, hemorrhage, hemodynamic instability, and alveolar lesions caused by the use of high fractions of inspired oxygen (FiO₂).¹ Thoracic surgeries are performed, for the most part, by placing the patient in the lateral

decubitus position with the nondependent hemithorax compressed by the surgical field, consequently the dependent lung is ventilated and the nondependent lung is not.⁹ Studies have revealed an inhibition of hypoxic pulmonary vasoconstriction (HPV) with volatile anesthetic agents, which gets compounded during OLV, and higher concentrations of volatile agents can lead to further blunting of this protective mechanism.

Dexmedetomidine is a new highly selective α_2 -adrenergic receptor agonist which has been used increasingly both in the intensive care unit and also peri-operatively as an adjunct to general anesthesia. Dexmedetomidine has been shown to reduce the dose of opioids, inhalational and intravenous anesthetics, thereby augmenting HPV, improve oxygenation during OLV through inhibiting oxidative stress and nitric oxide release.^{10,11}

In our study the mean fentanyl consumption for Dexmedetomidine group was $2.60 \pm 0.54 \mu\text{g.kg}^{-1}$ and in saline group was $3.05 \pm 0.56 \mu\text{g.kg}^{-1}$, which indicates low intraoperative opioid requirement in dexmedetomidine group (p-value 0.002). These results are comparable to observations made by Kerman S¹² et al, that patients receiving dexmedetomidine, had low intraoperative fentanyl requirements compared to placebo ($2.7 \mu\text{g/kg}$ versus $3.1 \mu\text{g/kg}$). Similar results were noted by other workers including, Lai Y¹³ et al and Ramanlal C¹⁴ et al, they concluded that dexmedetomidine minimizes intraoperative fentanyl requirement, in addition to attenuating surgical stress responses and maintains the hemodynamic stability when used as an adjuvant in general anesthesia. The mechanisms of the analgesic actions of α_2 -agonists have not been fully elucidated. A number of sites, both supraspinal and spinal, modulate the transmission of nociceptive signals in the CNS. Even peripheral α_2 -adrenoceptors may mediate anti-nociception.

Drugs may act at any of these sites to reduce nociceptive transmission, leading to analgesia.

The end tidal isoflurane was comparable in both the groups till 15 minutes of surgery (p-value > 0.05), thereafter the end tidal isoflurane was significantly reduced in dexmedetomidine group than saline group (p-value < 0.05). The end tidal isoflurane decreased from $1.23 \pm 0.162\%$ observed at 15 minutes to 0.73 ± 0.109 observed at 120

minutes which indicates that dexmedetomidine decreased isoflurane requirement, an observation which reiterates the anaesthesia sparing effects of dexmedetomidine. Moreover, bi-spectral index (BIS) was comparable in both the groups till 15 minutes of surgery (p-value > 0.05), following which BIS values were significantly reduced in dexmedetomidine group compared to saline group (p-value < 0.05), again indicating that dexmedetomidine decreases the BIS values for a given isoflurane concentration, hence decreasing the isoflurane requirement. Isoflurane was adjusted to maintain BIS of 40-60 throughout the study. Xia R¹⁵ et al, observed end tidal isoflurane to be significantly lower in dexmedetomidine group throughout the study as compared with placebo group ($p < 0.05$), however, BIS values were similar throughout the study in each group and between the two groups. Kerman S¹² et al observed dexmedetomidine administration decreased the expired concentration of desflurane required to maintain the bispectral index at 40-60 when compared with the control group ($4.5 \pm 0.8\%$ versus $5.1 \pm 0.8\%$).

Similar results were obtained by Aantaa R¹⁶ who studied the interaction of intravenous infusion of dexmedetomidine and isoflurane by using MAC of isoflurane as the measure of anesthetic potency. Their results indicated that MAC of isoflurane was 0.85% end tidal in control group, 0.55% end tidal with low dose of dexmedetomidine and 0.45% end tidal with high dose of dexmedetomidine. Mir G¹⁷ et al found that addition of dexmedetomidine to lidocaine in intravenous regional anesthesia shortened the onset times for both sensory and motor blockade and improved the quality of anesthesia, with prolonged postoperative analgesia time in superficial hand surgeries. Khan T¹⁸ et al also found that dexmedetomidine in doses of 5 μg as adjuvants to hyperbaric 0.5% bupivacaine intrathecally produced a significantly quick onset and longer duration of regional anesthesia (motor and sensory block) with benefit of prolonged postoperative analgesia.

Our study was not without limitations as the study was not blinded which might have added to observer bias. Also heart rate and blood pressure are crude markers for pain as other factors like fluid status, blood gases, surgical technique and drugs might have affected them.

CONCLUSION

There has been increasing use of dexmedetomidine in

various perioperative scenarios because of its beneficial physiological properties. There was a significant reduction in intraoperative fentanyl requirement in the group that received dexmedetomidine, together with a reduced isoflurane requirement. Overall dexmedetomidine infusion maintained better hemodynamic stability and allowed lower doses of opioids and anesthetics to be used.

DECLARATIONS

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