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Original Research Article

# A Randomized Placebo-Controlled Study to Evaluate the Efficacy of Nebulized Dexmedetomidine Premedication for Attenuation of Hemodynamic Stress Response during Laparoscopic Cholecystectomy under General Anesthesia

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**Abstract:**

**Background:** Intravenous dexmedetomidine is frequently used as an adjuvant in anaesthesia to provide hemodynamic stability during laparoscopic cholecystectomy; however, the role of nebulized dexmedetomidine for the same is not yet investigated. We aimed this study to determine the effect of nebulized dexmedetomidine administered as a premedication in attenuating the hemodynamic response during laparoscopic cholecystectomy as the primary objective while its effect on sevoflurane requirement, recovery profile and side effects as secondary objectives.

**Materials and Methods:** This prospective, randomized, placebo-controlled study included 60 patients of American Society of Anaesthesiologists (ASA) I and II aged 18-60 years of both gender undergoing laparoscopic cholecystectomy. They were randomized into two groups of 30 each to receive either nebulization with dexmedetomidine (1 mcg/kg in 5ml normal saline) in Group D and 5ml normal saline in Group C, administered 15 min before induction of general anaesthesia. Hemodynamic variables, sevoflurane requirement, Ramsay sedation score (RSS) and Modified Aldrete score were recorded preoperatively, and compared with t-test or chi-square test with $P<0.05$ as statistically significant.

**Results:** Mean arterial pressure and heart rate were significantly less in Group D as compared to Group C following intubation, pneumoperitoneum, surgery and extubation, $P<0.05$. Mean sevoflurane requirement (volume %) was significantly less in Group D (1.24±0.29%) as compared to Group C (2.69±0.28%), $P=0.001$, showing 53% reduction in Group D. Both groups were comparable regarding RSS scores, extubation time and recovery time, ($P>0.05$).

**Conclusion:** Administration of nebulized dexmedetomidine (1µg/kg) before induction provides hemodynamic stability and reduces sevoflurane requirement during laparoscopic cholecystectomy without any delay in recovery or side effects.

**Keywords:** Dexmedetomidine, Laparoscopic cholecystectomy, Nebulization, Hemodynamic stress response, Sevoflurane.



## Introduction

Laparoscopic cholecystectomy is the preferred approach to treat cholelithiasis nowadays owing to its advantages over open surgery like lesser pain, early mobilization, shorter hospital stay and better cosmetic results.

However, the laparoscopic procedure is not risk-free as it is associated with significant hemodynamic stress response due to combined effects of pneumoperitoneum, systemic absorption

of carbon dioxide, patient positioning, and anesthetic events of intubation and extubation. This may lead to increased arterial blood pressure, and systemic and pulmonary vascular resistance, along with decreased cardiac output which can be detrimental in susceptible individuals. [1] Different groups of drugs like vasodilators, beta-blockers, calcium channel blockers, opioids, volatile agents, α-2 agonists etc. have been used to attenuate this hemodynamic stress response with varied results.[2]

Dexmedetomidine, being a highly selective α-2 adrenergic agonist, possesses sympatholytic, sedative and analgesic properties therefore intravenous (IV) dexmedetomidine is routinely being used as an adjunct to anaesthesia during laparoscopic surgeries to maintain stable hemodynamics. Nevertheless, bradycardia, hypotension and delayed recovery may occur as side effects after its IV administration which are dose-dependent.[3,4] Hence, other routes of administration of dexmedetomidine are being investigated. The bioavailability of dexmedetomidine via nasal and buccal mucosa is reported to be 62% and 82% respectively making it a suitable agent to be administered via the nebulized route.[5]

Nebulized dexmedetomidine as a premedication has been successfully used to provide sedation and analgesia for various outpatient procedures in pediatric patients.[6,7] In some recent studies, the use of nebulized dexmedetomidine premedication was found effective in blunting hemodynamic pressor response and postoperative sore throat following tracheal intubation during general anesthesia in adults.[8-10] To the best of our knowledge, none of the studies has yet evaluated the role of nebulized dexmedetomidine in attenuating the hemodynamic stress response during laparoscopic cholecystectomy.

This prompted us to conduct the present study to test the hypothesis that the use of nebulized dexmedetomidine (1μg/kg) administered before induction of general anesthesia for laparoscopic cholecystectomy is effective in attenuating the hemodynamic stress response to critical periods of stimulation such as intubation, pneumoperitoneum, surgery and extubation as the primary objective and its effect on sevoflurane requirement, sedation, recovery profile, and side effects as secondary objectives.

## Materials and Methods

After obtaining approval from the institutional ethics committee (RNT/Stat./IEC/2021/465) and informed written consent from patients, this prospective, randomized, double-blind, placebo-controlled clinical study was carried out in 60 patients aged 18-60 years of both gender belonging to American Society of Anaesthesiologists (ASA) physical status I and II undergoing laparoscopic cholecystectomy under general anaesthesia (GA) from December 2021 to May 2022. Exclusion criteria were patient refusal, allergy to study drugs, predicted difficult airway, body mass index >30 kg/m2, pregnant female, ASA III or more, uncontrolled hypertension, severe cardiopulmonary, liver, kidney, endocrine, neurological or psychiatric disorders. The study was registered with the Clinical Trials Registry - India (CTRI/2021/11/037742). The study was done in accordance with the principles of the Declaration of Helsinki. Patients were randomly allocated into two groups of 30 each using a computer-generated random number table and allocation concealment sealed envelope technique. Patients in Group C (placebo control) received nebulization with 5 ml normal saline while patients in Group D (dexmedetomidine) received nebulization with dexmedetomidine (1 μg/kg) diluted with 5ml normal saline as a premedication 15min before induction of GA. The study drug used was dexmedetomidine hydrochloride 100 μg/ml (Inj Dexem 1 ml (100 μg), NEON Laboratories). For double blinding, drugs for nebulization were prepared by one anaesthesiologist who was not involved further in the study. The other anaesthesiologist who administered the drugs and recorded the data, patient and surgeon were unaware of group allocation.

All enrolled patients underwent a thorough pre-anesthetic evaluation along with routine investigations one day before surgery. Patients were explained about the study protocol and were kept nil per oral as per standard fasting guidelines. After arrival in the pre-anesthetic room, a peripheral 18G IV cannula was secured in the right upper limb and Ringer lactate 500 ml was started. Patients were nebulized via a nebulizer face mask using a wall-mounted continuous flow of oxygen-driven source (8L/min, 50 psi) ) for 10 min in a sitting position as per group allocation. Vital parameters i.e. heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), peripheral oxygen saturation (SpO2) and Ramsay sedation scale (RSS) score [11] were recorded before and after nebulization. In the operation theatre (OT), a multipara monitor was attached which included non-invasive blood pressure (NIBP), pulse oximetry (Sp$O_2$), electrocardiography (ECG), capnography ($EtCO_2$), anesthetic gas monitoring and bispectral index (BIS) and baseline values were recorded. Patients were Premedicated with IV Glycopyrrolate 0.2mg, midazolam 0.02 mg/kg, fentanyl 2 mcg/kg and ondansetron 4 mg. After pre-oxygenation with 100% $O_2$ for 3 min, induction was done using IV Propofol (2mg/kg) followed by IV succinylcholine 1-1.5mg/kg, and

after intermittent positive pressure ventilation with 100% O**2** for 1 min, the trachea was intubated with a cuffed endotracheal tube of appropriate size.

General anaesthesia was maintained with Vecuronium, sevoflurane, N2O and oxygen (50:50) with a target EtCO2 of 30-40 mmHg. Sevoflurane was titrated to maintain BIS in a range of 40-60 and MAP within 20% of baseline. After pneumoperitoneum creation with carbon dioxide, intraabdominal pressure was maintained between 12-14 mmHg and laparoscopic cholecystectomy was done using the standard surgical protocol. Sevoflurane was stopped when the scope was taken out of the abdominal cavity after the removal of the gallbladder. The residual neuromuscular blockade was reversed with neostigmine (0.04-0.08 mg/kg) and Glycopyrrolate (0.01 mg/kg) and the patient's trachea was extubated after meeting the extubation criteria. RSS was recorded after extubation every 2 min and patients were shifted to post anesthesia care unit (PACU) when RSS≤3. Modified Aldrete score [12] was recorded in PACU till a score of ≥ 9 was achieved, which was the criteria to shift the patients into the ward.

Hemodynamic parameters (HR, SBP, DBP and MAP) were recorded at the following specified time intervals i.e. at baseline before nebulization, after nebulization, before premedication in OT, after induction, immediately after intubation, 3 and 5 min after intubation, at the surgical incision, just after insufflation, and every 15 min thereafter, at exsufflation, just after reversal, just after extubation, then 5 and 10 min after extubation. Inspired volume % of sevoflurane was recorded after intubation at the same time interval as above to assess sevoflurane requirement. RSS was recorded before nebulization and after nebulization to assess preoperative sedation. RSS was also recorded immediately after extubation thereafter every 2 min till RSS≤2, to assess postoperative sedation. RSS11 was graded as:-1= Anxious and agitated or restless, 2= Cooperative, oriented, tranquil**,** 3 = Response to commands only**,** 4 =Asleep with brisk response to glabellar tap, 5 =Asleep with sluggish response to glabellar tap, 6=No response. Recovery profile was recorded as the time taken from stoppage of sevoflurane to tracheal extubation (Extubation time), and time taken from extubation to achieve a modified Aldrete score ≥9 (Recovery time).

Hypotension and bradycardia were defined as fall in MAP and HR >20% of baseline and treated with IV mephentermine 6 mg and IV atropine 0.6 mg respectively. Any other side effects, if occurred during the study period were noted and treated accordingly.

**Statistical Analysis**

None of the previous studies evaluated the efficacy of nebulized dexmedetomidine for attenuation of hemodynamic response after pneumoperitoneum hence sample size calculation was based on the pilot study conducted at same institute before commencement of our study that included 10 patients each in nebulized dexmedetomidine and control groups. Just after pneumoperitoneum, MAP was 98.75 ± 8.97 mm Hg in the nebulized dexmedetomidine group as compared to 107.48 ± 5.63 mm Hg in the control group. To detect a minimum difference of 6 mm Hg in MAP between two groups following pneomoperitoneum with 5% alpha error and 90% power, 26 patients were required in each group. To compensate for 10% dropouts and to comply with central limit theorem, we included 30 patients in each group hence 60 patients were enrolled in the present study. Data were analysed by using Statistical Package for Social Sciences (SPSS) version 20. Categorical (qualitative) data were presented as number (percentage) and continuous variables as Mean±SD (standard deviation) and were compared using the chi-square test and student t-test respectively, P<0.05 was considered statistically

**Results**

A total of 68 potentially eligible patients were screened for eligibility. Eight patients were excluded who did not fulfil the inclusion criteria (2 patients each having difficult airway, baseline MAP<60 mm Hg, HR<60 bpm and who declined to participate). Sixty confirmed eligible patients were included in the study who was randomized into two groups to receive the allocated intervention, completed follow-up and analysed with no drop outs (Figure 1).

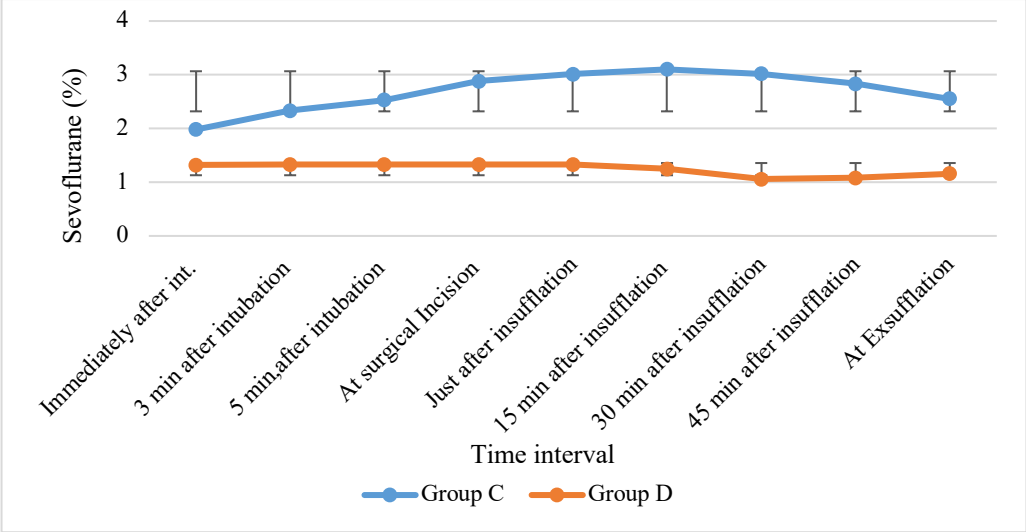


**Figure 2: Comparison of inspired volume % of sevoflurane in two groups**

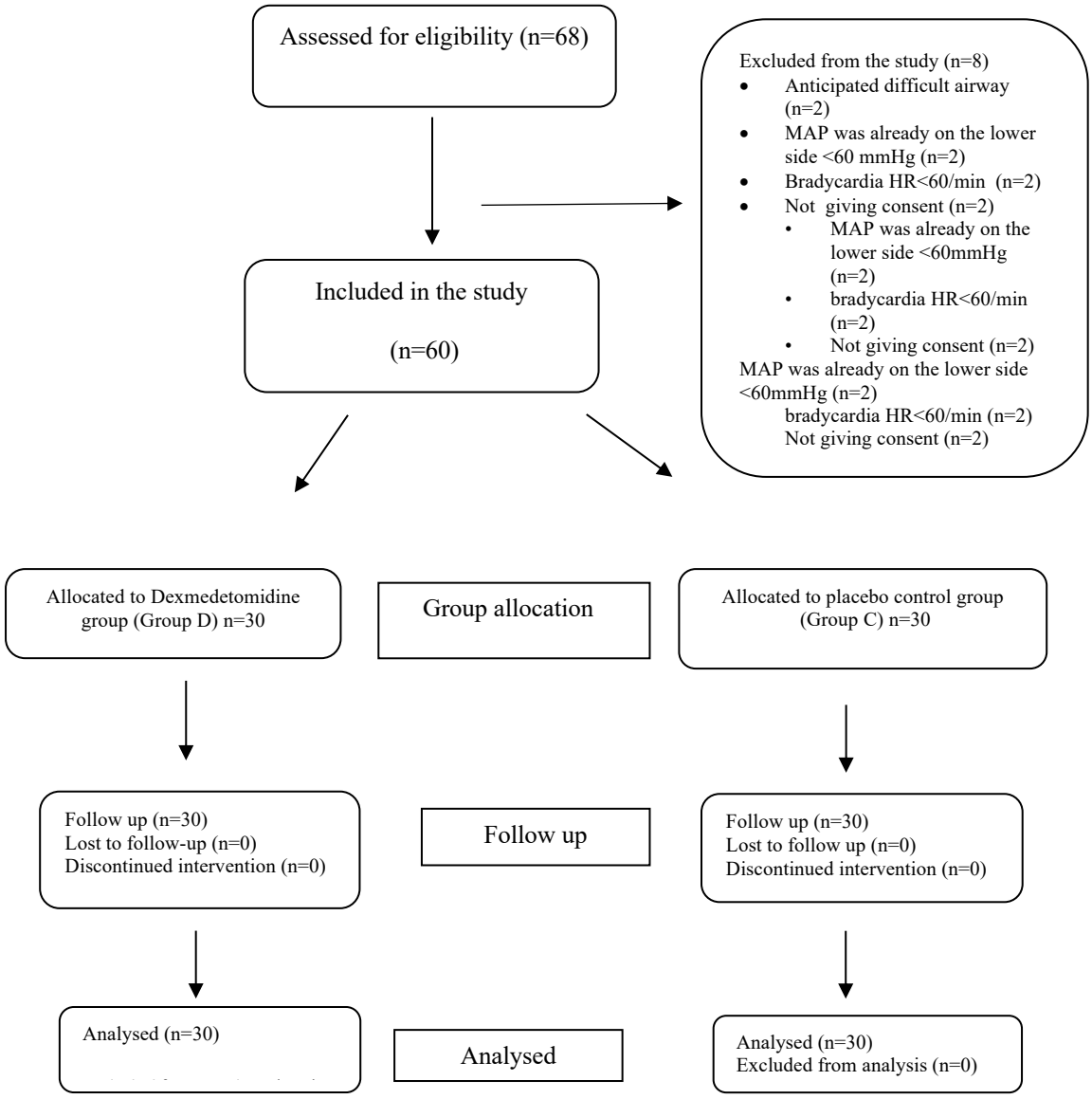


**Figure 1: CONSORT flow diagram**

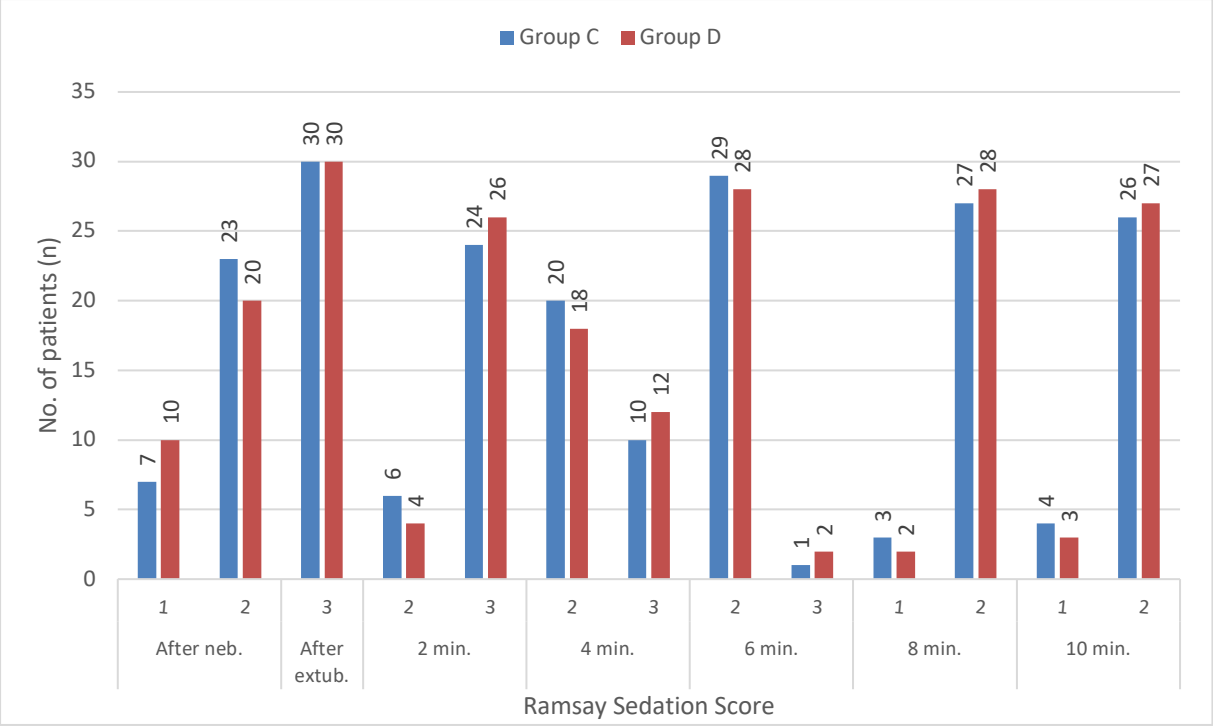


**Figure 3: Patient distribution according to Ramsay sedation score after nebulization and after extubation till 10 minutes in two groups**

**Table 1: Comparison of Demographic Profile, Duration of Surgery and Anaesthesia in two groups**

| Parameters | Group C (n=30) | Group D (n=30) | p value |
|---|---|---|---|
| **Age (years)** | 44.80±12.93 | 45.97±8.33 | 0.339 |
| **Weight (kg)** | 64.67±7.13 | 62.80±7.94 | 0.171 |
| **Height(cm)** | 157.43±2.51 | 156.20±3.70 | 0.137 |
| **Gender(Male/Female)** | 12/18 | 13/ 17 | 0.068 |
| **Duration of surgery (min)** | 51.16±16.52 | 56.20±9.50 | 0.07 |
| **Duration of anesthesia (min)** | 70.70±16.26 | 72.60±11.59 | 0.308 |

Data are presented as number (percentage) or Mean±SD, Statistical test used: chi-square test, Unpaired 't-test, p>0.05 (Not Significant)

**Table 2: Comparison of Mean Heart Rate (beats/min) and Mean Arterial Pressure (mm Hg) in two groups**

| Time Interval | HR | | | MAP | | |
|---|---|---|---|---|---|---|
| | Group C (n=30) | Group D (n=30) | p value | Group C (n=30) | Group D (n=30) | p value |
| **Baseline before nebulization** | 89.93±10.16 | 88.43±16.82 | 0.338 | 97.93±9.36 | 96.23±8.15 | 0.228 |
| **After nebulization** | 89.73±8.64 | 88.93±15.89 | 0.404 | 95.1±1.68 | 94.9±7.6 | 0.457 |
| **Before premedication in OT** | 90.90±6.96 | 89.17±15.29 | 0.287 | 97.7±6.71 | 94.43±8.34 | 0.053 |
| **After induction** | 90.06±7.10 | 85.03±15.59 | 0.056 | 88.4±6.13 | 85.8±7.72 | 0.071 |
| **Immediately after intubation** | *106.96±7.74 | *98.86±15.30 | #0.006 | *105.5±11.38 | 94.93±14.90 | #0.001 |
| **3 min after intubation** | *107.1±6.90 | *98.43±16.44 | #0.005 | *103.4±8.9 | 98.13±12.73 | #0.034 |
| **5 min after intubation** | *104.5±8.53 | *94.2±16.73 | #0.001 | *103.3±12.39 | 96.83±14.38 | #0.033 |
| **At surgical Incision** | *108.97±8.62 | *98.13±17.37 | #0.001 | *107.76±8.78 | 99.9±13.77 | #0.005 |
| **Just after insufflation** | *111.73±8.15 | *100.43±17.7 | #0.001 | *110.76±6.31 | 102.03±13.98 | #0.001 |
| **15 min after insufflation** | *109.07±9.22 | *97.63±16.63 | #0.008 | *105.73±10.23 | 98.23±14.5 | #0.012 |
| **30 min after insufflation** | *103.91±9.00 | 93.63±15.24 | #0.003 | *106.54±14.55 | 96.96±14.69 | #0.011 |
| **45 min after insufflation** | *100.33±11.25 | 88.33±12.07 | #0.029 | 97.44±4.30 | 89.23±8.86 | #0.009 |
| **At Exsufflation** | *100.1±8.65 | 90.86±14.30 | #0.001 | 100.5±11.17 | 95.53±9.02 | #0.031 |
| **Just after Reversal** | *109.47±7.51 | 96.63±15.82 | #0.000 | *117±8.62 | 99.73±6.31 | #0.000 |
| **Just after Extubation** | *108±8.33 | 95.5±12.03 | #0.001 | *110.9±15.86 | 100.73±9.13 | #0.043 |
| **After Extubation 5 min** | *101.13±8.69 | 91.7±13.03 | #0.000 | 100.13±9.6 | 94.63±10.85 | #0.012 |
| **After Extubation 10 min** | 93.87±7.12 | 87.03±9.92 | #0.001 | 95.1±7.34 | 89.33±7.83 | #0.029 |

Data are Mean±SD, *p<0.05, on intragroup variation from baseline (paired t-test), # p<0.05, on intergroup comparison (unpaired t-test)

Both groups were comparable regarding mean age, height, weight, gender, mean duration of surgery and anesthesia, P>0.05 (Table 1). Mean SBP, DBP, MAP and HR were comparable in two groups at baseline, post nebulization, before premedication in OT and after induction, P>0.05. On inter-group comparison, mean SBP, DBP, MAP and HR became significantly higher in Group C as compared to Group D just after intubation, and remained high at all-time intervals i.e. 3 min and 5 min after intubation, skin incision, immediately after gas insufflation, 15 min, 30 min and 45 min during surgery, at extubation, 5 min and 10 min after extubation, P<0.05. On intra group comparison mean SBP, DBP and MAP showed no significant variation from baseline at any point of time during the study in Group D,(P>0.05); while in Group C, mean SBP and MAP showed a significant rise from baseline, from intubation which persisted throughout surgery till extubation, P<0.05. Maximum % rise in SBP (10.6 % vs 3.7 %), DBP (3.1 % vs 1.6 %), MAP (13.1 % vs 6 %) and HR (24.2% vs 13.5%) from their baseline values were significantly higher in Group C as compared to Group D respectively which occurred immediately after gas insufflation for creation of pneumoperitoneum, P<0.05 (Table 2 and 3).

Mean inspiratory volume % of sevoflurane was significantly lower in Group D than in Group C at all-time intervals intraoperatively, P=0.00. Overall mean inspiratory sevoflurane volume % was significantly lesser in Group D (1.24±0.29 %) as compared to Group C (2.69±0.28 %),P=0.001. Mean sevoflurane requirement was decreased by 53% in Group D as compared to Group C,(Figure 2). Patient distribution according to RSS was comparable in two groups after nebulization and after extubation till 10 min, P>0.05,(Figure 3). Extubation time was comparable in Group C (9.43±1.07 min) and Group D (8.96±1.27 min), P=0.065. Recovery time was also comparable in Group C (9.86±1.04 min) and Group D (9.53±1.0min), P=0.106. In our study, no adverse effects were observed in the two groups.

**Discussion**

The present study showed that hemodynamic parameters i.e. mean HR, SBP, DBP and MAP were significantly less in the nebulized dexmedetomidine group as compared to the control group at all critical periods of stimulation like intubation, pneumoperitoneum, surgery and extubation. This proved our hypothesis that preoperative nebulization with dexmedetomidine (1 µg/kg) was effective in attenuating the hemodynamic stress response during laparoscopic cholecystectomy. Although nebulized dexmedetomidine is not approved yet by United States Food and Drug Administration (US-FDA), but as per available literature, many studies have been published in reputed journals where dexmedetomidine has been used via nebulization route both in adult [8-10,22] as well as pediatric [6,7,18] patients and it was found safe and effective.

Previous studies have also reported that nebulized dexmedetomidine (1 µg/kg) premedication was effective in attenuation of intubation pressor response and perioperative stress response in surgical patients in terms of rise in MAP and HR as compared to control groups, (P<0.05).[8-10] Intravenous dexmedetomidine has been administered as a bolus followed by infusion during laparoscopic cholecystectomy and significantly lower values of SBP, DBP, MAP and HR were reported at intubation, pneumoperitoneum and extubation than in control groups. [3,4,13-15] The hemodynamic effects of dexmedetomidine are attributed mainly to its central sympatholytic effect with a decrease in serum norepinephrine concentration. It acts on the locus ceruleus of the brainstem inhibiting sympathetic outflow and stimulating parasympathetic outflow. Its action on the kidney decreases plasma renin, increases glomerular filtration, and decreases sodium and water absorption thus producing diuresis. All the above actions lead to a dose-dependent decrease in arterial blood pressure and heart rate thus producing stable hemodynamic intraoperatively. [16,17]

In our study, sevoflurane requirement was significantly reduced in the dexmedetomidine group than in the control group. Misra et al [9] also reported a significant reduction in induction dose of Propofol (P<0.001), intraoperative fentanyl consumption (P=0.007) and isoflurane requirement (P=0.001) in the nebulized dexmedetomidine group. Kumar et al [8] also found a significant reduction in the induction dose of propofol in the nebulized dexmedetomidine group (1.17 mg/kg) as compared to the control group (1.45 mg/kg), (P=0.02). Various other studies also reported a significant reduction in anesthetic requirement in which IV dexmedetomidine was used in laparoscopic cholecystectomy. [3,4,13] Dexmedetomidine has a sedative, analgesic and anesthetic sparing effect due to its agonist action on α-2A receptor in locus ceruleus and spinal cord. [16,17]

No hypotension and bradycardia were observed in our study as well as in previous studies in which nebulized dexmedetomidine (1µg/kg) was administered as premedication in adult patients.[8-

10] However, bradycardia and hypotension were reported in pediatric patients in which comparatively higher doses of nebulized dexmedetomidine were administered to provide procedural sedation [6,18]. Anupriya et al [18] reported an incidence of hypotension (10.3%) with 2µg/kg and hypotension (13.3%) and bradycardia (3%) with 3µg/kg of nebulized dexmedetomidine. Similarly, Zanaty et al [6] reported an incidence of hypotension (10%) and bradycardia (10%) with 2µg/kg. The hemodynamic effects of dexmedetomidine are dose dependent.[16,17] A higher dose of dexmedetomidine along with higher vascularity and surface area of buccal cavity in pediatric patients resulted into higher plasma concentrations which might have caused adverse hemodynamic effects in above studies.[6,18] Bradycardia was observed as the most common adverse effect in studies where IV dexmedetomidine was used as a bolus followed by an infusion in laparoscopic cholecystectomy, with a reported incidence of 10% [4,19] and 14%. [3]

In our study, both groups were comparable regarding sedation scores after nebulization, after extubation and postoperative recovery profile. This corroborates with the findings of other authors who also reported no difference in sedation scores pre and post nebulization and post-extubation with no delay in recovery as compared to control groups after dexmedetomidine nebulization (1µg/kg) [8-10] On the contrary, many previous studies in which intravenous dexmedetomidine was administered to attenuate hemodynamic responses during laparoscopic cholecystectomy, relatively higher postoperative sedation scores and delay in recovery were observed. [4,13,20,21]

We want to highlight the fact that preoperative nebulization with dexmedetomidine in our study led to significantly better hemodynamic stability during laparoscopic cholecystectomy without producing adverse hemodynamic and sedative effects as found with intravenous dexmedetomidine. [3,4,19-21] This could be attributed to lower bioavailability (60-80%) of dexmedetomidine via nasal and buccal mucosa [5] as compared to the intravenous route causing lesser adverse hemodynamic and sedative effects with nebulized dexmedetomidine when used as a single dose (1µg/kg) in premedication in our as well as other studies.[8-10]

In addition to this, most of the studies [3,4,12,13] who administered IV dexmedetomidine as a bolus (1µg/kg) followed by infusion (0.2-0.5µg/kg/h), which was stopped at the time of removal of the trocar might have resulted in higher blood levels of dexmedetomidine that could be the reason of adverse hemodynamic effects, significant postoperative sedation and delayed recovery.

This finding is also supported by a study by Gu et al [22] who compared intravenous dexmedetomidine (0.6µg/kg) versus nebulized dexmedetomidine (0.6µg/kg) as an adjuvant to nebulized lidocaine in adult patients for flexible bronchoscopy. They also reported that recovery time in the nebulized group (10.60±1.49 min) was significantly shorter than that in an intravenous group (15.10±1.45 min), $p<0.001$. Requirement of ephedrine ($P<0.001$) and atropine ($P=0.029$) were also significantly more with intravenous dexmedetomidine as compared to nebulized dexmedetomidine.

There were a few limitations of our study. We did not use invasive arterial blood pressure monitoring which could demonstrate hemodynamic effects more accurately. The plasma levels of dexmedetomidine were not measured at different points of time intraoperatively which could be correlated with its observed pharmacological effects.

We have not measured the amount of sevoflurane consumed in millilitres per hour as it was not the primary objective of our study. Inspite of above limitations dexmedetomidine nebulization before induction seems to be a safe, effective, economical and easy to use technique to maintain stable hemodynamics during anesthesia for laparoscopic cholecystectomy.

## Conclusion

We conclude that administration of nebulized dexmedetomidine (1 µg/kg) before anesthesia induction was effective in attenuation of hemodynamic stress response to intubation, pneumoperitoneum, surgery and extubation during laparoscopic cholecystectomy along with reduced intraoperative sevoflurane requirement and without any delay in recovery or side effects.

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