Original Research Article

Clinical efficacy of dexmedetomidine in two different doses to attenuate the hemodynamic changes during laparoscopic cholecystectomy

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ABSTRACT

Background: Laryngoscopy and laparoscopy lead to predictable hemodynamic changes. Dexmedetomidine is selective 2 agonist with dose dependent sedation, sympatholysis and analgesia, hence could provide stable hemodynamics during laparoscopic surgeries. The present study was aimed to compare the clinical efficacy of dexmedetomidine infusion in two different doses to attenuate the hemodynamic variations during laparoscopic cholecystectomy.

Methods: Total 60 adult patients of ASA physical status I and II of both gender, scheduled for elective laparoscopic cholecystectomy, were randomly allocated into two groups of 30 patients. All patients were infused with loading dose of dexmedetomidine (1µg/kg) before induction. Patients of Group 1 received maintenance infusion of dexmedetomidine in doses of 0.3µg/kg/h and patients of Group 2 received maintenance infusion of dexmedetomidine in doses of 0.6µg/kg/h, continued till the end of surgery. Heart rate and blood pressure were recorded preoperatively, after dexmedetomidine administration, after induction, intubation, after creation of pneumoperitoneum and postoperatively. Intraoperative changes in heart rate and blood pressure were noted as primary variables and dexmedetomidine related side effects were noted as secondary outcomes, for statistical analysis.

Results: The hemodynamic responses were attenuated in patients of both groups after laryngoscopy, intubation and creation of pneumoperitoneum but patients of Group 2 (0.6µg/kg/h) showed more stability in hemodynamics. The difference between the group was statistically significant (p value=0.001). No any evident complication or side effects occurred.

Conclusions: Dexmedetomidine infusion was effective for attenuating the hemodynamic changes due to laryngoscopy and laparoscopy but were better with maintenance infusion of dexmedetomidine in dose of 0.6µg/kg/h.

Keywords: Dexmedetomidine, Hemodynamic changes, Laryngoscopy, Laparoscopic cholecystectomy, Pneumoperitoneum

INTRODUCTION

Laparoscopic cholecystectomy is advantageous due to cosmetically small scar, less postoperative pain, shorter hospital stays and early ambulation, but pneumoperitoneum leads to increase in plasma catecholamine levels, resulting increase in systemic and pulmonary vascular resistance, rise in arterial pressure and heart rate with reduced cardiac output. The reverse Trendelenberg position leads to significant hemodynamic and respiratory changes, thereby causing further reduction in cardiac output.1,2 Laryngoscopy with intubation also lead to transient and variable hemodynamic changes along with reflex sympathetic stimulation leading to peripheral sympathto-adrenal response.3
The magnitude of hemodynamic changes can be decreased by using different medical interventions, but each drug has its own limitations.\(^5\) Besides minimizing the cardiovascular response, the ideal agent must have a rapid onset of action, be safe and convenient to administer with desirable duration of action and also should not affect the recovery.

Dexmedetomidine, α-2 adrenergic agonist, inhibits the release of nor-epinephrine by presynaptic activation of the α-2 adrenoceptor in the locus coeruleus while post synaptic activation of α-2 adrenoceptor in the central nervous system resulted in decrease in sympathetic activity. Its intravenous use decreases the serum catecholamine levels by 90% and suppresses the hemodynamic response of laryngoscopy and laparoscopy. Dexmedetomidine, due to its various distinct properties, might be suitable medication during laparoscopic cholecystectomy.\(^6\)

The present study was aimed to compare the clinical efficacy of two different dosages of dexmedetomidine infusion to attenuate the hemodynamic changes during laryngoscopy, intubation and creation of pneumoperitoneum during laparoscopic cholecystectomy.

**METHODS**

After approval from Institutional Ethical Committee and written informed consent, 60 patients of American Society of Anesthesiologists (ASA) physical status I and II of either sex aged between 18 to 58 years, scheduled for elective laparoscopic cholecystectomy, were enrolled for the present double blind randomized study.

The patients suffering from cardio-pulmonary diseases, hepatic, renal or endocrinal disease, obesity, uncontrolled hypertension, any neurological disorder and patients with anticipated difficult airway or who required more than one attempt for intubation, were excluded from the studies. Patients with known hypersensitivity or drug allergies, taking any antihypertensive or antidepressant drugs, were also excluded from the study.

The total 60 patients were randomly assigned to two groups of 30 patients each, according to computer generated random number table. After the loading dose of dexmedetomidine (1.0µg/kg), patients of Group 1 were given maintenance infusion of dexmedetomidine in dose of 0.3µg/kg/h and patients of Group 2 were given maintenance infusion of dexmedetomidine in dose of 0.6µg/kg/h, continued till the end of surgery. Study drug preparation was done by an assistant who was blinded to the study protocol and was not involved for any data collection.

All patients underwent through preanesthetic evaluation along with relevant investigation. Patients were given tab alprazolam 0.25mg and tab ranitidine 150mg, the night before surgery and were kept fasting for 6 hours prior to surgery.

On arrival to operation theatre, baseline values of heart rate, non-invasive systemic arterial pressure, peripheral oxygen saturation (SpO2) and electrocardiogram (ECG) were recorded and lactate Ringer solution was started at the rate of 4-6ml/kg/h. All patients received glycopyrrolate 0.2mg IM half an hour before surgery and midazolam 1mg and ondansetron 4mg, intravenously. The loading dose of dexmedetomidine 1µg/kg, diluted in 10 ml normal saline, was infused over 10 minutes. Patients of Group 1 were given infusion of dexmedetomidine 0.3µg/kg/h and patients of Group 2 were given infusion of dexmedetomidine 0.6µg/kg/h, continued till the end of surgery.

After preoxygenation, anesthesia was induced with fentanyl 2µg/kg and propofol 2mg/kg and direct laryngoscopy was facilitated by vecuronium bromide 0.1 mg/kg. All patients were intubated with proper sized cuffed endotracheal tube and any patient requiring more than 20 seconds or more than one attempt, was excluded from the study. Anesthesia was maintained with isoflurane, nitrous oxide 60% in oxygen and vecuronium 0.02 mg/kg. Pneumoperitoneum was created by insufflations of carbon dioxide (CO2) and intra-abdominal pressure was maintained at 12mmHg. They were mechanically ventilated to keep the normocapnia (EtCO2 between 35-40mmHg). Patients were positioned in a 15° reversed Trendelenberg position and tilted towards the left side to facilitate exposure of the gall bladder.

After completion of surgery, patients were returned to supine position. Dexmedetomidine infusion was discontinued and residual neuromuscular blockade was antagonized by appropriate doses of neostigmine and glycopyrrolate and tracheal extubation was performed. The heart rate and arterial blood pressure were recorded at base line, after dexmedetomidine infusion, after induction and immediately after intubation. Then at regular intervals of 1st min, 2nd min, 3rd min, 4th min, 5th min, 7th min and 10th min, after tracheal intubation. Later on, these parameters were noted at regular intervals of 5 minutes till end of surgery and post extubation.

The hemodynamic changes observed as abnormal finding during the study were defined as hypotension when SBP <20% of baseline value or <90 mm of Hg, on two consecutive readings. Hypertension was defined as SBP> 20% of baseline value or>140 mm Hg. Tachycardia was defined as heart rate>100 beats/min and bradycardia were defined as heart rate < 60 beats/min.

The intraoperative hypertension and tachycardia was managed by increasing the dial concentration of isoflurane and hypotension was primarily treated by increasing the infusion rate of lactate Ringer solution and infusion of study medication was discontinued.

\(^{6,8}\)
Bradycardia was treated with intravenous atropine 0.5 mg bolus. Patients were transferred to post anesthesia care unit and monitored until there were no signs of any drug-induced effects. Any hemodynamic changes, respiratory depression, postoperative shivering, nausea and vomiting was noted and were treated accordingly.

Sample size and statistical analysis

Preliminary sample size was based on previous studies, which indicated that approximately 27 patients should be included in each group in order to ensure power of 80% and α-error of 0.05 with confidence limit of 95% for detecting clinically meaningful reduction by 20% in heart rate and blood pressure during laryngoscopy and laparoscopy. Assuming a 5% drop out rate, a total of 60 patients were incorporated in the study for better validation of results. The variables were expressed as Mean ±SD. The statistical analysis was done using Stat Graphics Centurion software version 17. The parameters were compared using the Chi-square test for categorical data, one-way analysis of variance (ANOVA) for intergroup comparison, and paired t-test for intragroup comparison. P-value <0.05 was considered statistically significant.

RESULTS

The present study was conducted on sixty adult patients of ASA physical status I and II of either sex. The demographic parameters of age, weight, height, gender ratio and ASA physical status were comparable between both the groups (Table 1). Baseline mean systolic blood pressure, diastolic blood pressure, and heart rate in patients of both groups were comparable.

Table 1: Demographic profile of the study population.

| Parameters          | Group 1          | Group 2          | P value |
|---------------------|------------------|------------------|---------|
| Age (years)         | 41.77±10.99      | 40.23±8.7        | 0.54    |
| Weight (kg)         | 59.17±5.5        | 60.43±9.3        | 0.525   |
| Height (cm)         | 159.97±3.8       | 160.83±4.5       | 0.427   |
| Gender (M/F)        | 18/12            | 21/9             | 0.659   |
| ASA (I/II)          | 24/6             | 23/7             | 0.098   |

Data are presented as Mean ± SD or absolute numbers. P value >0.05 is statistically insignificant

Changes in heart rate

The mean heart rate decreased significantly below the baseline value after starting the dexmedetomidine infusion. No further significant changes were noticed immediately after induction of anaesthesia. After intubation, the heart rate increased significantly above the baseline values in patients of Group 1 but heart rate did not increased in patients of Group 2. The difference between the groups showed statistically significant till 7th minute after intubation. Later on, the changes in mean heart rate were comparable between the groups (Table 2).

Table 2: Changes in heart rate at different time intervals.

| Heart rate (beats/min) | Group 1       | Group 2       | P value |
|------------------------|--------------|--------------|---------|
| Baseline               | Mean±StDev   | Mean±StDev   |         |
| 98.64±13.21            | 97.88±11.70  |              | 0.029   |
| After dexmedetomidine  | 96.92±12.48  | 98.88±12.54  | 0.269   |
| After induction        | 94.71±6.70   | 92.04±4.20   | 0.329   |
| Just after intubation  | 93.71±8.70   | 91.04±5.28   | 0.846   |
| 1 min                  | 90.12±7.07   | 90.01±8.02   | 0.392   |
| 2 min                  | 87.96±7.08   | 87.6±7.01    | 0.396   |
| 3 min                  | 85.32±7.71   | 77.36±7.30   | 0.0001**|
| 4 min                  | 85.76±7.66   | 73.12±6.35   | 0.0001**|
| 5 min                  | 83.12±6.28   | 72.4±5.32    | 0.0001**|
| 7 min                  | 84.4±8.22    | 72.92±6.71   | 0.0001**|
| 10 min                 | 83.92±5.46   | 83.84±5.12   | 0.451   |
| 15 min                 | 87.96±7.08   | 87.6±7.01    | 0.564   |
| 20 min                 | 86.32±7.47   | 76.36±7.40   | 0.0001**|
| 30 min                 | 85.6±7.61    | 74.12±6.36   | 0.0001**|
| 45 min                 | 83.12±6.28   | 82.4±5.32    | 0.393   |
| 60 min                 | 89.71±8.92   | 82.04±5.28   | 0.795   |
| 75 min                 | 80.22±7.07   | 80.14±8.10   | 0.465   |
| 90 min                 | 87.96±7.08   | 87.6±7.01    | 0.555   |
| Post extubation        | 86.32±7.47   | 86.16±7.40   | 0.657   |

Data are presented as Mean ± SD. P value <0.001 is statistically highly significant.
Changes in systolic blood pressure

After dexmedetomidine infusion, induction and intubation, there was a continuous gradual reduction in mean systolic blood pressure in patients of both groups with statistically highly significant difference at 1st, 5th, and 10th min following laryngoscopy and intubation (p=0.000).

After creation of pneumoperitoneum, the changes in mean systolic blood pressure were comparable between the groups till post extubation (Table 3).

Table 3: Changes in systolic blood pressure at different time intervals.

| Systolic BP (mmHg) | Group 1 | Group 2 | P value |
|--------------------|---------|---------|---------|
|                    | Mean    | Std. Deviation | Mean    | Std. Deviation |         |
| Baseline           | 134     | 9.9      | 136     | 9.2       | 0.413   |
| After dexmedetomidine premedication | 131 | 10.7 | 131 | 10.0 | 0.532 |
| After induction    | 129     | 7.3      | 126     | 7.4       | 0.0001*** |
| Just after intubation | 130   | 6.4      | 126     | 6.2       | 0.0001** |
| 1 min              | 130     | 7.8      | 124     | 7.2       | 0.0001** |
| 2 min              | 129     | 7.6      | 123     | 7.3       | 0.0001** |
| 3 min              | 130     | 6.2      | 126     | 7.4       | 0.0001** |
| 4 min              | 129     | 7.1      | 123     | 6.5       | 0.0001** |
| 5 min              | 122     | 11.6     | 122     | 9.5       | 0.438   |
| 7 min              | 121     | 10.8     | 120     | 9.0       | 0.582   |
| 10 min             | 128     | 7.4      | 122     | 6.7       | 0.0001** |
| 15 min             | 130     | 7.4      | 126     | 6.5       | 0.0001** |
| 20 min             | 122     | 11.2     | 121     | 8.1       | 0.857   |
| 30 min             | 121     | 11.6     | 122     | 8.5       | 0.985   |
| 45 min             | 121     | 10.8     | 120     | 9.0       | 0.191   |
| 60 min             | 120     | 9.4      | 118     | 8.8       | 0.664   |
| 75 min             | 120     | 10.7     | 118     | 9.5       | 0.489   |
| 90 min             | 122     | 11.2     | 121     | 8.1       | 0.958   |
| Post extubation    | 122     | 12.5     | 124     | 9.9       | 0.854   |

Data are presented as Mean ± SD. P value <0.001 is statistically highly significant

Table 4: Changes in diastolic blood pressure at different time intervals.

| Diastolic BP (mm Hg) | Group 1 | Group 2 | P value |
|----------------------|---------|---------|---------|
|                      | Mean    | Std. Deviation | Mean    | Std. Deviation |         |
| Baseline             | 81.8    | 7.8      | 82.73   | 7.0       | 0.958   |
| After dexmedetomidine premedication | 88.2  | 8.7 | 81.47 | 7.7 | 0.155 |
| After induction      | 80.27   | 7.8      | 72.34   | 6.9       | 0.0001** |
| Just after intubation | 77.27  | 7.8      | 71.4    | 6.9       | 0.0001** |
| 1 min                | 78.31   | 8.2      | 72.33   | 6.2       | 0.0001** |
| 2 min                | 77.73   | 6.3      | 72.87   | 6.1       | 0.0001** |
| 3 min                | 76.27   | 6.8      | 75.47   | 6.2       | 0.931   |
| 4 min                | 76.8    | 6.8      | 75.2    | 5.7       | 0.463   |
| 5 min                | 75.07   | 7.8      | 74.4    | 4.8       | 0.110   |
| 7 min                | 77.53   | 7.2      | 73.9    | 6.1       | 0.0001** |
| 10 min               | 77.03   | 8.0      | 73.73   | 6.6       | 0.0001** |
| 15 min               | 74.67   | 6.1      | 71.73   | 6.3       | 0.946   |
| 20 min               | 74.67   | 6.2      | 73      | 7.9       | 0.931   |
| 30 min               | 78.07   | 6.0      | 74.4    | 6.7       | 0.626   |
| 45 min               | 79.8    | 5.7      | 77      | 5.6       | 0.611   |
| 60 min               | 80.94   | 6.9      | 74.2    | 5.2       | 0.601   |
| 75 min               | 81.06   | 7.0      | 72.1    | 6.2       | 0.527   |
| 90 min               | 74.67   | 6.2      | 73.1    | 7.9       | 0.789   |
| Post extubation      | 74.7    | 6.2      | 73.1    | 7.8       | 0.491   |

Data are presented as Mean ± SD. P value <0.001 is statistically highly significant
**Changes in diastolic blood pressure**

There was a gradual decrease in diastolic blood pressure after administration of dexmedetomidine, after induction and intubation with statistically significant difference between the groups, but after creation of pneumoperitoneum and post extubation, the fall in diastolic blood pressure was comparable between the groups (Table 4).

**Changes in mean arterial pressure**

There was significantly lower mean arterial pressure in patients of Group 2 when compared to Group 1, after induction, till 2nd minutes after intubation and then after 30th min till post extubation (Table 5).

### Table 5: Changes in mean arterial pressure at different time intervals.

| Mean arterial pressure (mmHg) | Group 1 | Group 2 | P value |
|------------------------------|---------|---------|---------|
|                              | Mean    | Std. Deviation | Mean    | Std. Deviation |         |
| Baseline                     | 89.47   | 7.6      | 92.83   | 7.5      | 0.985   |
| After dexmedetomidine premedication | 87.33   | 8.4      | 90.97   | 7.2      | 0.699   |
| After induction              | 89.5    | 8.7      | 79.37   | 8.2      | 0.001** |
| Just after intubation        | 89.5    | 8.4      | 81.37   | 8.1      | 0.001** |
| 1 min                        | 85.1    | 8.4      | 77.6    | 7.5      | 0.001** |
| 2 min                        | 83.5    | 7.0      | 78.47   | 6.9      | 0.001** |
| 3 min                        | 80.97   | 7.5      | 79.7    | 8.3      | 0.687   |
| 4 min                        | 79.1    | 7.8      | 77.6    | 7.1      | 0.126   |
| 5 min                        | 78.07   | 7.0      | 78.4    | 7.8      | 0.577   |
| 7 min                        | 78.57   | 7.3      | 77.4    | 8.0      | 0.207   |
| 10 min                       | 79.1    | 6.7      | 77.2    | 7.0      | 0.855   |
| 15 min                       | 79.97   | 7.8      | 77.3    | 7.8      | 0.351   |
| 20 min                       | 80.57   | 7.5      | 77.13   | 7.5      | 0.187   |
| 30 min                       | 86.6    | 8.3      | 79.7    | 8.4      | 0.001** |
| 45 min                       | 89.3    | 7.4      | 77.6    | 7.5      | 0.001** |
| 60 min                       | 90.1    | 9.1      | 78.47   | 6.9      | 0.001** |
| 75 min                       | 88.2    | 8.9      | 79.7    | 8.3      | 0.001** |
| 90 min                       | 87.42   | 7.3      | 77.6    | 7.1      | 0.001** |
| Post extubation              | 88.11   | 9.4      | 78.57   | 8.1      | 0.001** |

Data are presented as Mean ± SD. P value <0.05 is statistically significant, P value <0.001 is statistically highly significant.

### Adverse events

Two patients of Group 2 developed bradycardia (Heart Rate = 55 beats/min), which occurred just after the dexmedetomidine infusion (0.6 µg/kg/h), but it increased after laryngoscopy, so no treatment was given. There were no other postoperative complications related to dexmedetomidine or anaesthetic technique occurred during study period.

### DISCUSSION

Pneumoperitoneum during laparoscopic cholecystectomy leads to complex pathophysiological changes including significant hemodynamic variation and pulmonary physiology which compromise tissue perfusion. Direct laryngoscopy and intubation also leads to a hypertensive pressor response due to reflex sympathetic discharge. Though these hemodynamic changes are short lived but may be undesirable in patients with preexisting myocardial or cerebral insufficiency. Tachycardia is poorly tolerated in patients with coronary heart disease. Moreover, the reverse Trendelenberg position during laparoscopic cholecystectomy further enhance the cardiovascular and pulmonary function.

The pharmacological approach is appropriate for attenuation of hemodynamic changes during laparoscopic surgery. Opioid analgesics, intravenous lidocaine, beta adrenergic blockers, α2 adrenergic receptor agonists, and vasodilators were studied to attenuate these hemodynamic events.

Dexmedetomidine is highly selective α2-adrenergic receptor agonist with a shorter duration of action. It minimizes the increase in heart rate and blood pressure by decreasing the central sympathetic outflow, thus modify the intraoperative cardiovascular responses to laryngoscopy and laparoscopic surgical stimuli. The significance of study lies in the fact that, which dosages of dexmedetomidine infusion could safely and effectively attenuate the hemodynamic changes, neither affecting the duration or modality of the anaesthetic technique nor has any effect on the recovery of patients. Dexmedetomidine in doses of 0.3 µg/kg, 0.4 µg/kg, 0.5 µg/kg, 0.6 µg/kg, 0.8 µg/kg and 1 µg/kg have been studied by various
authors to find the effective and safe dose but with conflicting results.10-12

For the present study, two different doses of dexmedetomidine infusion (0.3µg/kg/h and 0.6µg/kg/h) were chosen, to be given after loading dose of dexmedetomidine (1µg/kg) which was administered slowly over 10 minutes. Rapid administration of initial loading dose of dexmedetomidine was avoided to prevent the transient increase in blood pressure and reflex decrease in heart rate.

The primary action of dexmedetomidine on heart is negative chronotropic effect by blocking the cardio-accelerator nerves as well as by augmenting the vagal nerve. The decrease in heart rate can be attributed to reflex response for transient hypertension during initial part of infusion and subsequently it was due to diminish nor-epinephrine release and inhibition of central sympathetic outflow.13,14

In the present study, there was a gradual reduction in heart rate after dexmedetomidine administration in patients of both groups with no significant difference. After induction, there was decrease in systemic blood pressure in all patients, but the decrease was more in patients who received dexmedetomidine infusion in higher dose (0.6µg/kg/h), with statistically significant difference. Other workers also observed the similar results.

After intubation, there was increase in mean heart rate in patients of both groups which can be attributed to the increase in the central sympathetic outflow. Dexmedetomidine was effective for suppressing the rise in heart rate. The results of present study are similar with the studies conducted by Kunisawa et al and Sagiroglu et al.15,16 They stated that dexmedetomidine infusion blunts the hemodynamic changes of intubation and higher doses of dexmedetomidine caused greater reduction in the heart rate.

After creation of pneumoperitoneum, the changes in heart rate showed statistically significant difference between both the groups at 20 minute. The present study was in accordance with the studies done by Basar et al.17

Bhattachargy et al evaluated the efficacy of dexmedetomidine in patients undergoing laparoscopic cholecystectomy. They observed significantly lower mean arterial pressure and heart rate in patients of dexmedetomidine group after intubation and throughout the period of pneumoperitoneum. Dexmedetomidine has improved the intra and post-operative hemodynamic stability during laparoscopic surgery without prolongation of recovery.18 The present study was in accordance of their study.

Yildiz M et al and Varshali MK et al studied the effect of dexmedetomidine on hemodynamic responses to laryngoscopy, intubation and on anesthetic requirement.19,20 They concluded that increase in blood pressure and heart rate were significantly lower in dexmedetomidine group than in placebo group. Sajith et al showed statistically significant difference in systolic, diastolic and mean arterial pressure between dexmedetomidine group and control group at 1st, 3rd, and 5th minute post extubation in their study.21

Bakhamees HS et al studied the effect of dexmedetomidine on morbidly obese adult patients, undergoing laparoscopic gastric bypass, by giving 0.8µg/kg bolus of dexmedetomidine, followed by dexmedetomidine infusion in dose of 0.4µg/kg/h. They concluded that the intraoperative infusion offered a better control of intraoperative and postoperative hemodynamics.22

The results of the present study were in accordance with these previous clinical studies. They all found significant difference in fall in heart rate and systolic blood pressure in patients who received intraoperative dexmedetomidine infusion in higher dosages.

Dexmedetomidine has offered a unique pharmacological profile with sedation, analgesia, sympatholysis and cardiovascular stability by attenuating the stress induced sympatho-adrenal responses to intubation and pneumoperitoneum during surgery.

CONCLUSION

The present study concluded that dexmedetomidine infusion in dose of 0.6µg/kg/h, after the loading dose of dexmedetomidine (1µg/kg), appeared to be significantly more effective for attenuating the hemodynamic changes of laryngoscopy, tracheal intubation and pneumoperitoneum during laparoscopic cholecystectomy.

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