

## Comparative Study of Preanesthetic Single dose Dexmedetomidine versus Placebo in Patients Undergoing Elective Laparoscopic Cholecystectomy

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### Abstract

**Background:** Laparoscopic surgery is a routinely performed surgery and it is desirable to have a stable intraoperative haemodynamic states by avoiding hypertension and tachycardia. **Aim:** The present study has been conducted to compare the beneficial effect of alpha2 adrenergic receptor agonist dexmedetomidine versus placebo in maintaining the perioperative haemodynamic parameters during laparoscopic cholecystectomy. **Materials and Methods:** The present Randomized double blind comparative study was conducted in the Department of Anaesthesiology. A total of 60 patients randomly allocated in two groups, to Group D (Dexmedetomidine) & Group P (Placebo) of 30 each undergoing elective laparoscopic cholecystectomy, under GA were studied. The patients received preloaded and coded study drug as infusion (Dexmedetomidine 0.5 mcg/kg & NS 10 ml) before induction. **Results:** Sex, age, and weight were comparable in the two groups. The study drug dexmedetomidine maintained cardiovascular stability during laparoscopic cholecystectomy. Mean arterial pressure and heart rate in Group D (Dexmedetomidine) were significantly less after intubation and throughout the period of pneumoperitoneum. In addition, other drugs requirement in placebo group was found to be considerably high when compared to dexmedetomidine group. **Conclusion:** Dexmedetomidine improves intraoperative and postoperative haemodynamic stability during laparoscopic surgery without prolongation of recovery. Dexmedetomidine was more effective in attenuating hemodynamic response to intubation and pneumoperitoneum when compared with placebo.

**Keywords:** Dexmedetomidine; Placebo; Elective Laparoscopic Cholecystectomy

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### Introduction

Laparoscopic surgeries involves insufflation of a CO<sub>2</sub> gas into the peritoneal cavity producing a pneumoperitoneum. This causes an increase

in intra-abdominal pressure. Carbondioxide is insufflated into the peritoneal cavity at the rate of 4-6 lit/min to a pressure of 10-15 mm Hg. [1] The pneumoperitoneum is maintained by a constant gas flow of 200-400 mL/min. Peritoneal insufflation induces alterations of haemodynamics,

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characterized by decrease in stroke volume and cardiac output, elevation of mean arterial pressure, and increase of systemic and pulmonary vascular resistance [2]. Haemodynamic changes are accentuated in high-risk cardiac patients. General anaesthesia has been supplemented on occasions with intraoperative infusions of propofol due to its intrinsic ability to inhibit catecholamine secretion, infusions of nitroglycerine or beta blockers to control perioperative stress. Again combined GA with epidural anaesthesia is yet another strategy employed by anaesthesiologists to control perioperative haemodynamic instability, with limited success. But the search for the ideal agent to control this instability in haemodynamics is still on [3]. The pathophysiologic haemodynamic changes can be attenuated or prevented by optimizing preload before pneumoperitoneum and by vasodilating agents,  $\alpha_2$ -adrenergic receptor agonists, high doses of opioids, and  $\beta$ -blockers. Alpha 2 agonists produce diverse responses including analgesia, anxiolysis, sedation and sympatholysis, each of which has been reported in the treatment of surgical and chronic pain patients and in panic disorders as well. The food and drug administration (FDA) registered two novel  $\alpha_2$ -adrenergic agonists Clonidine and Dexmedetomidine. The  $\alpha_2$  agonists, including clonidine and dexmedetomidine, decrease central sympathetic outflow and modify intraoperative cardiovascular responses to surgical stimuli and laryngoscopy. The reduction in tachycardia, hypertension, and sympathetic activity may be of benefit in patients at risk of myocardial ischemia. Clonidine is a centrally acting selective partial  $\alpha_2$  agonist (220:1  $\alpha_2$ :  $\alpha_1$ ) with a elimination half-life of 6-10 hours. It is known to induce sedation, decrease anaesthetic day requirement and improve perioperative haemodynamics by attenuating BP & HR responses to surgical stimulation and protection against perioperative myocardial ischemia. It provides sympathoadrenal stability and suppresses renin angiotensin activity. Dexmedetomidine is an  $\alpha_2$  adrenergic receptor agonist with high selectivity for the  $\alpha_2$  receptor ( $\alpha_2$  to  $\alpha_1$  1620:1) and it is seven to ten times more selective for  $\alpha_2$  receptors compared to clonidine, and has a shorter duration of action with a elimination half-life of 2-3 hours. Dexmedetomidine is considered full agonist at  $\alpha_2$  receptors as compared to clonidine, which is considered as a partial agonist. The purpose of this study was to compare the effects of a single IV dose of dexmedetomidine by administering 10 minutes before induction of anesthesia with placebo group on induction and haemodynamic parameters

in patients undergoing elective laparoscopic cholecystectomy.

### Materials and Methods

The present study conducted from 1<sup>st</sup> September 2014 to 1<sup>st</sup> June 2015. The study protocol was approved by the Institutional Ethical committee and informed consent was taken from each of the patients. It was prospective, randomized and double blinded study. The study included total 60 patients belonging to ASA grade I and II of either sex with age between 20-55 years posted for laparoscopic cholecystectomy. A prospective, randomized, double blind comparative study consisting of 30 patients in group D (Dexmedetomidine) and 30 patients in group P (Placebo group) is undertaken to compare the haemodynamic parameters in patients undergoing elective laparoscopic cholecystectomy, requirement of rescue drugs and adverse effects. A sample size of 30 patients each, randomly allocated into two groups, using computerized randomization.

*Inclusion Criteria* was patients planned for elective laparoscopic cholecystectomy surgery, age group of 20-55 years and ASA I and II patients.

*Exclusion criteria* was patients unwilling for the study, patients who had hypertension and diabetes, obese with BMI greater than 30, ASA III, IV, V patients, patients with cardiovascular, pulmonary, hepatic, neurological and endocrine abnormalities, pregnant patients, known case of pre-op hypotension, surgeries converted to open cholecystectomy, inability to understand protocol due to language barrier, hypersensitivity to dexmedetomidine.

A Pre-anaesthetic evaluation comprising of history of previous medical and surgical illnesses, previous anaesthetic exposures, drug allergies; and baseline investigations of blood, radiograph of the chest and airway examination will be done. Informed written consent will be taken from the patient. Patient will be kept nil by mouth for at least 6 hours prior to surgery. Preoperative vital parameters in the form of baseline pulse, blood pressure and oxygen saturation will be recorded. NIBP, pulse oximeter, EtCO<sub>2</sub>, ECG, anaesthesia machine was checked, resuscitation equipment and drugs were checked and kept ready, before undertaking the procedure. On arrival to operation theatre, routine monitors (ECG, Pulse oximetry, NIBP) attached and baseline vital parameters like heart rate, mean arterial blood pressure (MAP) and arterial oxygen

saturation (SpO<sub>2</sub>) were recorded. An intravenous line with 18G secured. After baseline parameters were noted, patients were allocated randomly to the two groups using a computer generated random numbers table. An anesthesiologist who was not one of the study participants prepared syringes containing either dexmedetomidine or 0.9% saline. Both syringes were labeled "study drug" and coded to maintain the double-blinded nature of the study. Dexmedetomidine 0.5 µg kg<sup>-1</sup> was prepared in a 10-mL isotonic solution and 10-mL isotonic 0.9% normal saline was taken and labeled as study drug. All patients premedicated with Fentanyl 2 µg/kg, Glycopyrrolate 4 µg/kg, Ondansetron 15 µg/kg were given slowly intravenously, 20 minutes before induction. Patients in Group D received Dexmedetomidine 0.5 µg/kg by IV infusion, 10 minutes before induction. Patients in Group P received 10 ml of 0.9% normal saline by IV infusion, 10 minutes before induction. All patients were preoxygenated with 100% O<sub>2</sub> for 3 minutes and were induced with Propofol 2 mg/kg IV. Intubation was facilitated by using Vecuronium bromide 0.1 mg/kg. The lungs were ventilated with 100% oxygen for 3 minutes. Intubation was achieved with an appropriate size oral cuffed, portex endotracheal tube by the aid of Macintosh laryngoscope blade. CO<sub>2</sub> was insufflated into the peritoneal cavity (at a rate of 2 lit/min) to create pneumoperitoneum. Intra-abdominal pressure was restricted to 10-14 mmHg throughout the laparoscopic procedure. The patients were mechanically ventilated to keep ET CO<sub>2</sub> between 35-40 mmHg. Anaesthesia was maintained with Vecuronium bromide and intermittent positive pressure ventilation with nitrous oxide and oxygen in the ratio of 50:50 with 1% Isoflurane using circle absorber system connected to the Boyle's anesthetic work station. The parameters recorded were heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SpO<sub>2</sub>, EtCO<sub>2</sub>. The recordings were noted at various intervals from the study conducted; pre-operatively i.e. before pre-medication, after induction, after intubation, 15 mins, 30 mins, 45 mins, 60 mins, 75 mins, 90 mins, extubation, post op first hour.

*Statistical analysis:* The data was expressed as mean and standard deviation. The homogeneity in two groups of mean and standard deviation was analysed using SPSS version, Analysis of variance (ANOVA) for each parameter. Comparison between two groups at a time (inter-group comparison) was done using student's unpaired t- test. p <0.05 was considered statistically significant, value < 0.01 was considered highly significant, > 0.05 was considered insignificant.

## Results

A total of 60 patients randomly allocated in two groups, to Group D (Dexmedetomidine) & Group P (Placebo) of 30 each undergoing elective laparoscopic cholecystectomy, under GA were studied. Sex, age, and weight were comparable in the two groups.

Table 1 shows that There were no significant differences between the two groups with regard to demographic data such as age, sex, and weight. Both groups have a sex ratio which are comparable. The average age in Group D (Dexmedetomidine) was 38.06 years and average age in Group P (Placebo) was 41.56 years. The average weight in Group D (Dexmedetomidine) was 64.06 kgs and average weight in Group P (Placebo) was 67.5 kgs. Both the groups were comparable with respect to demographic profile. No significant differences were found with respect to age, sex, and weight.

Figure 1 shows that heart rates were on lower side in Group D (Dexmedetomidine) after induction, intubation, pneumoperitoneum and maintained throughout the intraoperative and post-operative period compared to Group P (Placebo). There is highly significant difference in heart rate between both groups during intraoperative and post-operative period. Heart rate significantly lower in Group D compared to Group P throughout the intraoperative period.

Figure 2 shows that systolic blood pressure(SBP) is lower in Group D patients after induction,

Table 1: Demographic profile (Mean ± SD):

| Characteristics | Group D               | Group P               | p value | Significance |
|-----------------|-----------------------|-----------------------|---------|--------------|
| Age in years    | 38.067 ± 7.306        | 41.567 ± 6.961        | 0.062   | NS           |
| Sex (F:M)       | 13:17 (1.433 ± 0.504) | 10:20 (1.333 ± 0.479) | 0.434   | NS           |
| Weight          | 64.067 ± 8.642        | 67.5 ± 9.347          | 0.145   | NS           |
| Sex (Female)    | 13 (43%)              | 10 (33.33%)           |         |              |
| Male            | 17 (57%)              | 20 (66.67%)           |         |              |

NS-Non Significant

intubation, 15 mins, 30 mins, 45 mins and 60 mins after pneumoperitoneum and throughout the intraoperative period and post operative recovery period compared to Group P. In Group P Systolic blood pressure (SBP) is higher in preoperative, intraoperative period and post operative recovery period compared to Group D.

Figure 3 shows that in Group D (Dexmedetomidine), DBP (Diastolic blood pressure) is significantly lower during intubation, 15 mins after pneumoperitoneum, extubation and in the post operative method compared to Group P (Placebo).

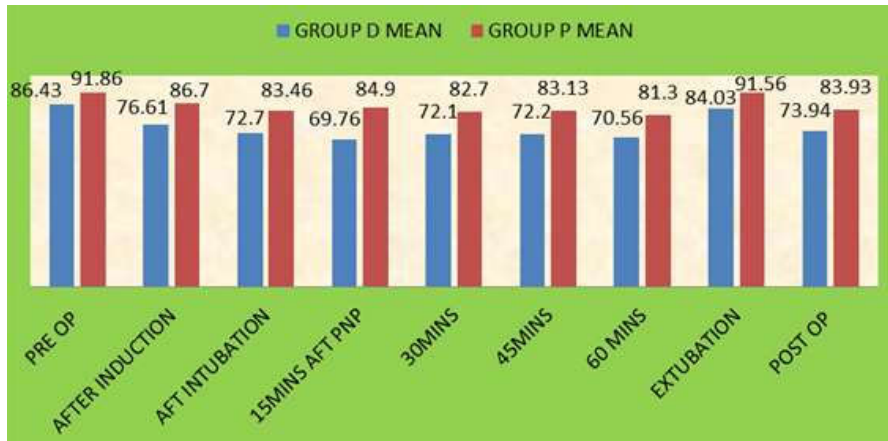


Fig. 1: Changes in heart rate

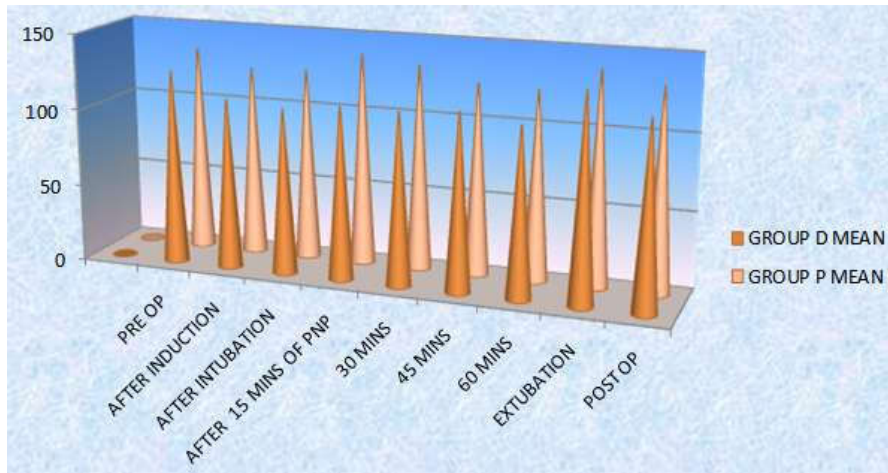


Fig. 2: Changes in systolic blood pressure (Mean ± SD)

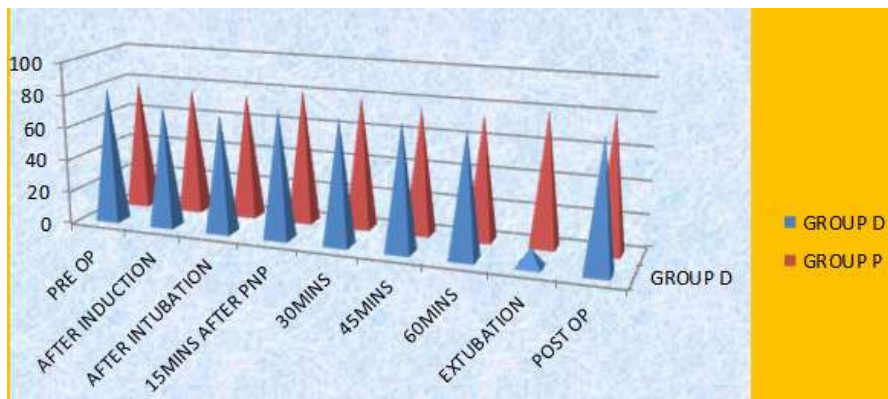


Fig. 3: Changes in DBP (Mean)

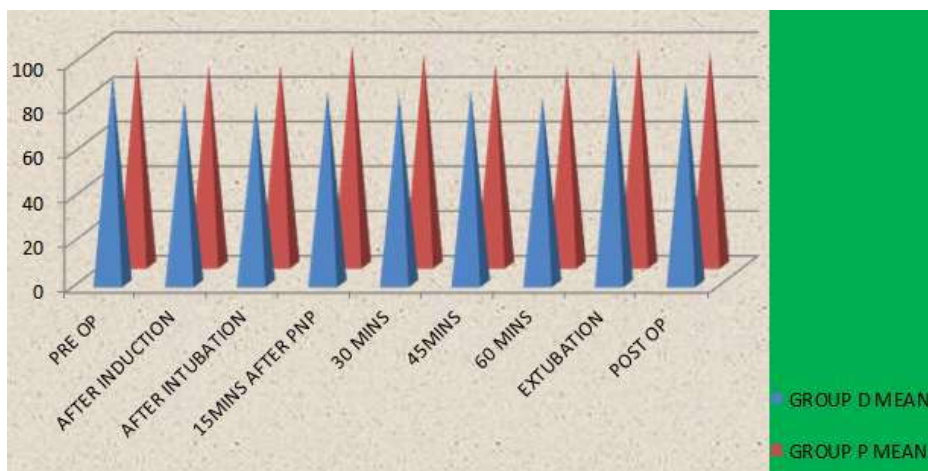


Fig. 4: Changes in mean arterial pressure (Mean ± SD)

Figure 4 shows that mean arterial pressure (MAP) is lower in Group D patients after induction, intubation, 15 mins, 30 mins, and 60 mins after pneumoperitoneum and in the post operative recovery period. In Group P patients, mean arterial pressure (MAP) is higher compared to Group D after induction, intubation pneumoperitoneum and throughout the intraoperative period. There was no significant difference in the preoperative Mean values of MAP between the two groups. MAP values in group D were significantly lower after induction than in group P ( $p < 0.05$ ). MAP values in group D were highly significantly lower ( $p < 0.01$ ) after intubation and pneumoperitoneum and remained lower throughout the pneumoperitoneum and in the postoperative period.

Table 2: Recovery time following extubation.

| Time (Mins)                              | Group D (Mean ± SD) | Group P (Mean ± SD) | p value  |
|--|---------------------|---------------------|----------|
| Ability to vocalize following extubation | 3.7667 ± 1.8880     | 6.1667 ± 1.4404     | < 0.0001 |

Table 2 shows that ability to vocalize following extubation was significantly prolonged in Group P (Placebo) when compared to Group D (Dexmedetomidine). In our study, a single dose of  $0.5 \mu\text{g kg}^{-1}$  of dexmedetomidine given preoperatively 10 minutes before induction led to significant sedation, but it does not caused delay in the recovery time following extubation. It caused delay in recovery time in Group P, when compared to Group D due to higher consumption of isoflurane, to maintain haemodynamic stability after creation of pneumoperitoneum and throughout the intraoperative period.

Table 3: Comparison of adverse effects between two groups.

| Adverse Effects | Group D (N=30) | Group P (N=30) |
|-----------------|----------------|----------------|
| Bradycardia     | 0 (0%)         | 0 (0%)         |
| Hypotension     | 0 (0%)         | 2 (6.6%)       |

Table 3 shows that the study didn't encountered episodes of bradycardia in any case of both the study groups. But we have seen two cases of hypotension in our placebo group (Group P).

In Group D other drugs like Inj.Paracetamol has been used only for 4 cases for additive analgesia and it clearly explains that dexmedetomidine is highly effective in providing adequate analgesia throughout the intraoperative period. In Group P other drugs like clonidine, metoprolol have been used in 28 cases to maintain haemodynamic stability throughout the intraoperative period after creation of pneumoperitoneum. p value is less than 0.0001 and is highly significant.

### Discussion

In the present study, we compared the effects of dexmedetomidine and placebo administered before induction on haemodynamic parameters in patients undergoing elective laparoscopic cholecystectomy. In laparoscopic surgery,  $\text{CO}_2$  is routinely used to create pneumoperitoneum. Elevated intra abdominal pressure induced by pneumoperitoneum and  $\text{CO}_2$  itself produce some adverse effects on the cardiovascular system. In the present study, found statistically significant changes between Group D (Dexmedetomidine) and Group P (Placebo) as regards to heart rate, mean arterial pressure after induction, intubation, 15 mins, 30 mins, 45 mins, 60 mins after pneumoperitoneum,

and throughout intraoperative period and in post operative period, changes in heart rate and mean arterial pressure were found to be significant. The present study confirms that haemodynamic changes (rise in mean arterial pressure and heart rate) are attenuated by dexmedetomidine infusion given 10 minutes before induction during laparoscopic cholecystectomy. The decrease in heart rate appears more in the Group D (Dexmedetomidine) at all intervals when compared to Group P (Placebo), but the fall was found to be significant. Similarly the fall in mean arterial pressure (MAP) appeared more in Group D (Dexmedetomidine) compared to Group P (Placebo) and the fall was found to be significant. In present study, we didn't encountered episodes of bradycardia and hypotension in any case of Group I (Dexmedetomidine). In the present study, requirement of other drugs was very less in Group D (Dexmedetomidine) as it maintained stable haemodynamics and adequate analgesia throughout the intraoperative period. In Group P (Placebo) requirement of other drugs was very high to maintain haemodynamic stability throughout the intraoperative period. Various studies have been conducted with various pharmacological interventions that results in reduced incidence of tachycardia, hypertension during laparoscopic cholecystectomy and provide a stable haemodynamic state, without significant undesirable effects.

In a study, Jaakola et al. [4] found decreased BP and HR during intubations following the administration of 0.6 µg/kg bolus of dexmedetomidine preoperatively. In our study, we found significant fall in HR after intubation with a mean of (72.70) in Group D (Dexmedetomidine) compared to Group P (Placebo) with a mean of (83.46) and significant fall in MAP after intubation with a mean of (81.33) in Group D (Dexmedetomidine) compared to Group P (Placebo) with a mean of (89.90). In a study, Lawrence and De Lange [5] found decreased hemodynamic response to tracheal intubation or extubation following a single high dose of dexmedetomidine (2 µg/kg). In our study, we found decreased hemodynamic response to tracheal intubation or extubation following a single dose of dexmedetomidine (0.5 µg/kg) given in infusion over 10 mins before induction. In a study, Ghodki et al. [6] used dexmedetomidine 1 µg/kg intravenously over 15 min before induction followed by maintenance infusion of 0.2 µg/kg/h and observed favorable vasopressor response during laryngoscopy, with minimal change in BP with pneumoperitoneum. In our study, we used single dose of dexmedetomidine 0.5 µg/kg in infusion

over 10 mins before induction, and observed hemodynamic stability after laryngoscopy, intubation, and pneumoperitoneum. In a study, Dutta et al. [7] showed that when propofol, another induction agent was used, dexmedetomidine decreased the propofol concentration necessary for sedation by approximately 60% to 80%. In a study, Aho et al. [8] found that opioid requirement decreases following 0.4 µg kg<sup>-1</sup> dexmedetomidine. Plasma noradrenaline concentration was markedly reduced in patients receiving dexmedetomidine. This decrement in neuronal noradrenaline release may explain in part the reduction in thiopental requirements. The response to thiopental is shown by three clinical signs: loss of eyelid reflex, loss of corneal reflex, and absence of movement in response to squeezing the trapezius muscle. The eyelid reflex was lost at significantly lower levels of thiopental than the corneal or movement response. The presence of an endotracheal tube leads to reflex sympathetic responses during both intubation and extubation. Sympathetic responses include hypertension, tachycardia, increased intraocular and intracranial pressures, bronchospasm, and myocardial ischemia. The use of α<sub>2</sub> agonists in the preoperative period has been associated with attenuated HR and BP responses to stressful events.

In a study, Jaakola et al. [4] showed that dexmedetomidine attenuated the increase in HR and BP during intubation. In our study, single-dose 0.5 µg/kg preoperative dexmedetomidine given in infusion, and maintained hemodynamic stability after intubation and in the intraoperative period. In a study, Lawrence et al. [5] found that a single dose of dexmedetomidine before induction of anesthesia attenuated the hemodynamic response to intubation and extubation. They used a large dose (2 µg kg<sup>-1</sup>) of dexmedetomidine; bradycardia was observed on the first and fifth minutes after administration. In our study, single-dose 0.5 µg/kg preoperative dexmedetomidine given in infusion, maintained hemodynamic stability after intubation, extubation and in the intraoperative period, without causing bradycardia in any one of our study cases. In a study, O'Leary E, Hubbard K et al. [9] studied hemodynamic and neuroendocrine responses after pneumoperitoneum, and changes in position in laparoscopic cholecystectomy and concluded that there were much hemodynamic fluctuations with rise in BP and HR due to catecholamine release. In our study dexmedetomidine showed a favorable outcome in Group I (Dexmedetomidine) patients. Dexmedetomidine decreased BP and HR during pneumoperitoneum. thus, maintaining haemodynamic stability. In a study,

According to Bhattacharjee et al. [10], effects of dexmedetomidine 0.2 µg/kg/hr were studied in sixty patients undergoing elective laparoscopic cholecystectomy. Mean arterial pressure and heart rate were significantly less after intubation and throughout the period of pneumoperitoneum. In our study too, MAP and HR were significantly less after intubation and throughout the period of pneumoperitoneum. In a study Yildiz M, Tavlan A, Tuncer S, Reisli R et al. [11], studied effects of dexmedetomidine on haemodynamic responses to intubation on fifty patients scheduled for elective minor surgery were randomised into two groups (dexmedetomidine group and placebo group, n = 25 in each group. Fentanyl 1 microg/kg was administered to all patients and thiopental was given until lash reflex disappeared. Anaesthesia continuation was maintained with 50%:50%, oxygen : nitrous oxide. Haemodynamic parameters and adverse effects were recorded every 10 minutes for 1 hour after surgery. Arterial blood pressure and heart rate in intraoperative period were significantly lower in the dexmedetomidine group compared with the placebo group (p < 0.05). In our study, a single dose 0.5 µ/kg of Dexmedetomidine administered before induction resulted in blunting of haemodynamic responses during laryngoscopy, and reduced opioid and anaesthetic requirements. Tufanogullari B, White PF, et al. [12] studied effect of Dexmedetomidine infusion during laparoscopic bariatric surgery and the effect on recovery outcome variables. There was significant difference in MAP and heart rate between two groups during intraop and postop period with favourable outcome with dexmedetomidine. In our study, we found similar results. There was significant difference in MAP and heart rate between both groups during intraoperative period. It can be concluded that dexmedetomidine provides a good haemodynamic stability by attenuating haemodynamic response during laparoscopic cholecystectomy.

### Conclusion

To conclude, dexmedetomidine reduces the elevation of mean arterial pressure and heart rate during and after pneumoperitoneum and thereby improving perioperative haemodynamic stability during laparoscopic surgery. The haemodynamic stability provided by dexmedetomidine should be helpful in patients with compromised cardiac function by allowing these patients to get the benefits of the laparoscopic approach. In our study,

we found that in Group D (Dexmedetomidine), the heart rate and MAP remained similar to the preoperative value during pneumoperitoneum (PNP), thus indicating the haemodynamic stability during PNP with Dexmedetomidine group when compared to Group P (Placebo group).

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