# Effects of Intramuscular Dexmedetomidine as Premedication in Elective Laparoscopic Surgeries - A Prospective Randomized Controlled Study in Trichy, Tamilnadu

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**ABSTRACT**

**BACKGROUND**

The major concern of laparoscopic surgery is intra-operative hypercapnia induced stress response such as increase in heart rate (HR), increase in blood pressure (BP), increased stress hormones. The major concern of anaesthetist is to reduce stress response perioperatively. Drugs like clonidine, dexmedetomidine, nitroglycerine and esmolol are used to control the hemodynamic response associated with pneumoperitoneum in laparoscopic surgeries. Dexmedetomidine has been found to have hemodynamic stability with good analgesic effect. Dexmedetomidine is a highly selective $\alpha_2$ agonist with sedative, analgesic and sympatholytic properties. Here in this prospective randomized controlled study, we evaluate the effects of intramuscular dexmedetomidine as a premedication in laparoscopic cholecystectomy.

**METHODS**

This is a randomized controlled study. Forty patients aged 20 to 50 years, both sexes, with American society of anaesthesiology (ASA) grade I & II planned for elective laparoscopic cholecystectomy were randomly assigned into two groups, Group DS : (N - 20) Received 2 mcg/kg of dexmedetomidine with normal saline (total 2 ml) Group CS : (N - 20) Received 2 ml of normal saline as intramuscular injection in the deltoid region 60 minutes before induction. We compared the hemodynamic parameters like pulse rate, mean arterial pressure (MAP) in baseline, preinduction, during intubation, before and after carbon dioxide insufflation, post extubation, visual analog score (VAS) and the analgesic requirements in both groups.

**RESULTS**

Compared to control group, intramuscular dexmedetomidine group had statistically significant reduction in pulse rate, mean arterial pressure perioperatively during intubation, before and after carbon dioxide insufflation, during surgery and post extubation ($P < 0.001$) and also found to decrease the analgesic requirement post operatively.

**CONCLUSIONS**

2 mcg/kg intramuscular dexmedetomidine premedication produces better hemodynamic stability, reduced perioperative analgesic requirement and hence could be a better alternative to other premedicant agents.

**KEYWORDS**

Dexmedetomidine, IM Premedication, Laparoscopy, Stress Response

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## BACKGROUND

Nowadays many advanced techniques have been emerging in the field of surgery, from conventional procedure to minimal or less invasive surgeries like laparoscopy, arthroscopy, and endoscopic spine surgery. One among the best advances is laparoscopic surgery. Advantages are less blood loss, better wound healing, rapid return of gastrointestinal function, less post-operative respiratory complication, lesser duration of hospital stay and early mobilisation. Most of the hospitals are using carbon dioxide for creating pneumoperitoneum, which has its own advantage and disadvantage. The main advantages are it does not support combustion, and absorbed carbon di oxide is eliminated via respiration from the blood. The major disadvantage is hypercapnia, which can stimulate sympathetic nervous system causing hemodynamic changes like tachycardia, increased systemic and pulmonary vascular resistance and hypertension. It is of major concern in elderly people and patient with compromised cardiac status.

The hemodynamic disturbances in laparoscopic surgeries are not only due to pneumoperitoneum, but also with patient positioning, anaesthetic technique and hypercapnia. Higher intra-abdominal pressure will worsen the hemodynamic changes. The safest and most commonly used anaesthetic technique for laparoscopic surgery is general anaesthesia with controlled ventilation. Our aim is to reduce both the intubation and extubation stress response, as well as to alleviate the hemodynamic consequences of hypercapnia, pneumoperitoneum with the added advantage of post-operative pain relief. Drugs like clonidine, dexmedetomidine, nitroglycerine and esmolol are used to control the hemodynamic response associated with pneumoperitoneum in laparoscopic surgeries.

Dexmedetomidine is a highly selective alpha$_2$ agonist. It is 8 to 10 times more selective towards alpha$_2$ receptors than Clonidine. Stimulation of alpha$_{2A}$ receptors in locus ceruleus inhibits nociceptive neurotransmission in the descending medullospinal noradrenergic pathway and causes analgesia.[1] Stimulation of post synaptic activation of alpha$_{2A}$ receptors in the CNS causes sympatholytic effect leading to hypotension and bradycardia. Activation of alpha$_{2C}$ receptor causes anxiolytic effect.[2] Dexmedetomidine also reduces the shivering threshold by 2$^o$ C.[3]

Many studies have been done using IV dexmedetomidine as premedicant in laparoscopic surgeries to attenuate the stress response associated with pneumoperitoneum and carbon dioxide induced hypercapnia and they have reported frequent episodes of bradycardia with IV dexmedetomidine.[4-7] Hence, we formulated a new study to evaluate the hemodynamic effects of intramuscular dexmedetomidine.

### Objectives

1. To determine the effects of intramuscular dexmedetomidine as a premedication in patients undergoing laparoscopic surgery on perioperative haemodynamics
2. To compare the perioperative analgesic requirements and pain score among patients undergoing laparoscopic surgery with intramuscular dexmedetomidine premedication and controls.

## METHODS

The study was conducted in Trichy SRM Medical College Hospital and Research Centre, Irungalur, Trichy, Tamilnadu, India from June 2018 to February 2020. This study was a single centre, prospective, randomized, comparative and observer blinded study. We obtained the ethical committee approval from our institution and the reference number is 407 / TSRMMCH & RC / IEC – No 135. Written informed consent was obtained from the patients in their own language. Forty patients aged between 20 - 50 years with American society of anaesthesiology Grade I & II undergoing elective laparoscopic cholecystectomy were included in this study. Patients were excluded from the study if they had difficult airway, baseline heart rate less than 60 per minute, diabetes mellitus, cardiac disease, respiratory disease, neurological disorder, impairment of hepatic and renal functions.

All the study participants were shifted to the pre-operative room where the baseline pulse rate, blood pressure and saturation were noted. The patients were randomly allocated into two groups according to computer generated random numbers and group allocation was done using sealed envelope technique. Participants in Group DS received 2 mcg/kg dexmedetomidine with normal saline (total 2 ml) intramuscularly, and the participants in Group CS received 2 ml normal saline intramuscularly in the deltoid region 60 minutes before induction. To ensure blinding, the medical staff administering injection and the attending anaesthesiologist was unaware of the content of the drug.

Patients were preloaded with 500 ml Ringers lactate. After entering into operation theatre, ECG, pulse oximeter, non-invasive BP monitors were connected. Before induction pulse rate, systolic blood pressure, diastolic blood pressure and saturation were recorded. After preoxygenation with 100 percent oxygen for 3 minutes, patients in both groups were induced with inj. fentanyl 2 mcg/kg IV and inj. propofol 2 mg/kg IV slowly. After confirming the ability to mask ventilate, patients were paralysed with inj. vecuronium (0.08 mg/kg). Pulse rate, systolic blood pressure, diastolic blood pressure and saturation were again documented as post induction hemodynamic parameters. 3 minutes after giving vecuronium, tracheal intubation proceeded with the appropriate size endotracheal tube. ET tube position was confirmed with ETCO2, equal bilateral air entry. Pulse rate, mean arterial blood pressure, saturation were noted 1 minute and 5 minutes after intubation.

Patients were ventilated with tidal volume of 8 ml per kg of ideal body weight and respiratory rate at 12 to 14 per minute. Anaesthesia was maintained with isoflurane (0.8 %) with nitrous oxide and oxygen mixture as 2 : 1 and inj. vecuronium 0.01 mg/kg intravenous intermittently. Intra-abdominal pressure was maintained less than 12 mmHg.

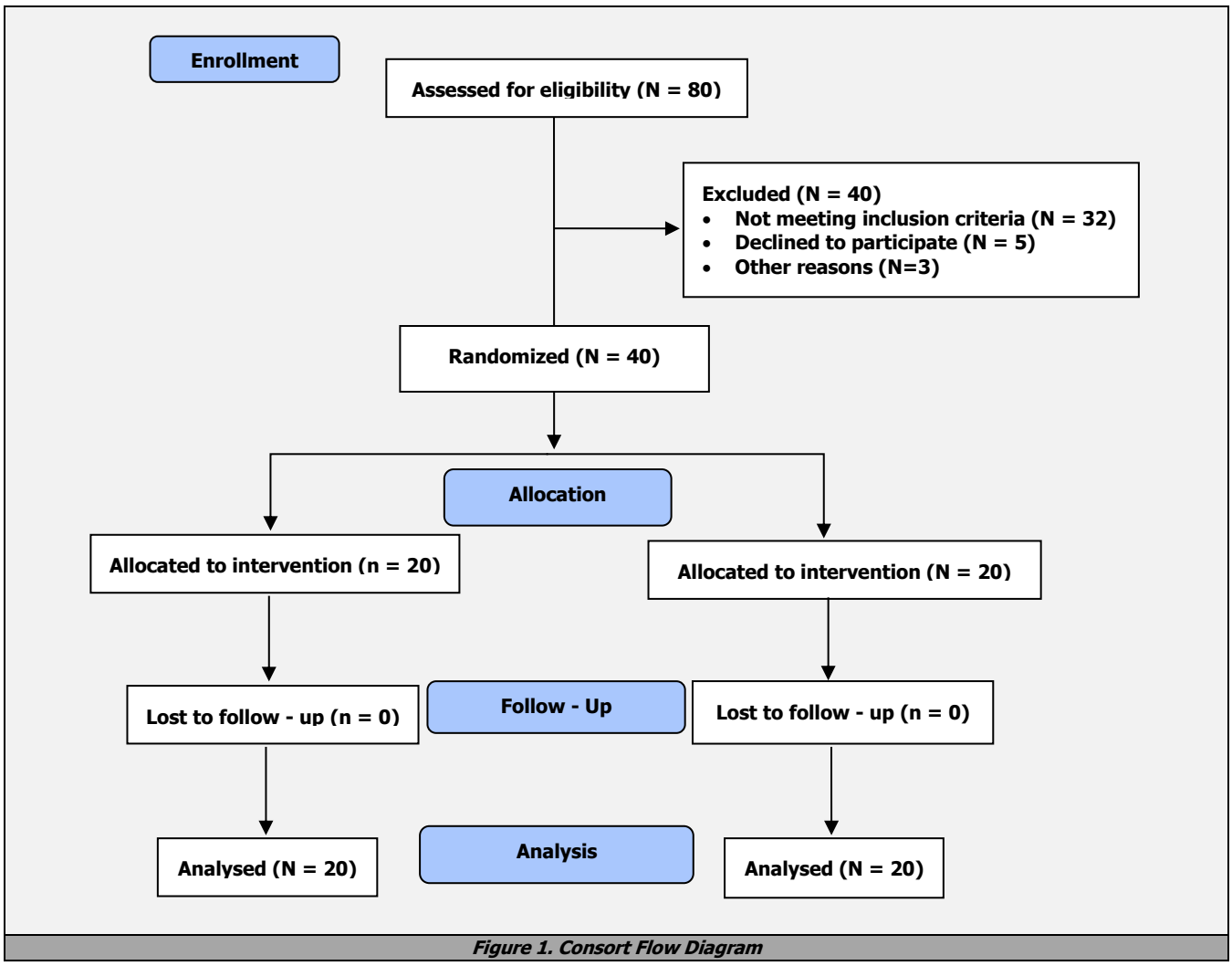


***Figure 1. Consort Flow Diagram***

Again, the pulse rate, mean arterial pressure were documented just before pneumoperitoneum, 5 min, 10 min, 20 min, 30 min, 45 min after pneumoperitoneum. Signs of inadequate anaesthesia (HR > 20 % and MAP > 20 % of preinduction values) were managed with inj. propofol 20 mg in titrated dose and bradycardia (< 50/min) was treated with Inj. glycopyrrolate 0.2 mg.

Other parameters such as requirement of propofol boluses, post-operative analgesic requirement, dryness of mouth, post-operative shivering were recorded. At the end of the surgery residual neuromuscular block was reversed with inj. neostigmine 50 mcg/kg with inj. glycopyrrolate 10 mcg/kg IV. After regaining protective reflexes and spontaneous respiratory effort, patient was extubated. Again, the pulse rate, mean arterial pressure was recorded 1 min, 5 min 15 min & 30 min after extubation.

Pain was assessed with visual analogue scoring system at the end of the surgery, 30 min, 60 min, 90 min, 2nd hour, 4th hour after surgery. Inj. paracetamol 15 mg/kg IV was given for the patients with VAS more than 5.

### Statistical Analysis

According to Kalpana S Vora et al. study, considering a mean difference in reduction of heart rate between dexmedetomidine and saline group as 10 beats per minute ($\mu_1 - \mu_2$) and an average standard deviation of reduction of heart rate in both groups as 10 beats per minute (σ), at 95 % confidence interval ($Z_{1-\alpha/2} = 1.96$) with 80 % power ($Z_{1-\beta} = 0.84$), the sample size is calculated as $N = Z_{1-\alpha/2} + Z_{1-\beta})^2 * 2 * \sigma^2 / (\mu_1 - \mu_2)^2$ = ( 1.96 + 0.84) ² * 2 * 10² / 10 ² = 16.[8] The sample size is rounded off to 20 per group and the total sample size is 40. Data was analyzed with SPSS version 21.

All data were expressed in mean ± SD. The data were analysed by chi - square test and student's t - test. A P - value of < 0.05 was considered statistically significant.

## RESULTS

| | | Group DS | | Group CS | | P |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | Value |
| Age (years) | | 25.75 | 3.508 | 25.6 | 5.220 | 0.894 |
| Sex | Male | 12 (60 %) | | 11 (55 %) | | |
| | Female | 8 (40 %) | | 9 (45 %) | | |
| Weight (kg) | | 53.9 | 3.575 | 53.55 | 5.196 | 0.833 |
| Duration of surgery (min) | | 57.7 | 6.658 | 58.50 | 6.581 | 0.654 |
| Duration of anaesthesia (min) | | 74.1 | 7.833 | 74.60 | 7.437 | 0.892 |

***Table 1. Demographic and Descriptive Data***

The distribution of age, sex, weight, duration of surgery and anaesthesia between the two groups were statistically not significant. (P >0.05) (Table 1) The duration of surgery is considered as the time between skin incision for port entry to skin closure in minutes. The duration of anaesthesia is

considered as the time between induction to extubation in minutes.

| Pulse Rate | Group DS | | Group CS | | P Value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Baseline | 82.85 | 5.102 | 83.45 | 4.430 | 0.712 |
| Pre induction | 71.50 | 4.425 | 89.90 | 1.940 | 0.001 |
| Post induction | 71.50 | 2.395 | 92.10 | 2.340 | 0.001 |
| 1 min after intubation | 87.60 | 2.644 | 120.45 | 6.262 | 0.001 |
| 5 min after intubation | 87.25 | 2.531 | 117.50 | 3.940 | 0.001 |
| Before pneumoperitoneum | 79.85 | 3.066 | 113.65 | 6.243 | 0.001 |
| 5 mins after pneumoperitoneum | 77.95 | 4.395 | 96.70 | 5.253 | 0.001 |
| 10 min after pneumoperitoneum | 75.05 | 4.651 | 92.10 | 2.337 | 0.001 |
| 20 min after pneumoperitoneum | 72.45 | 2.212 | 96.25 | 1.916 | 0.001 |
| 30 min after pneumoperitoneum | 71.80 | 1.852 | 95.55 | 1.852 | 0.001 |
| 45 min after pneumoperitoneum | 72.20 | 1.240 | 96.65 | 2.084 | 0.001 |
| 1 min after extubation | 92.05 | 3.663 | 120.50 | 3.317 | 0.001 |
| 5 min after extubation | 78.95 | 3.980 | 107.10 | 3.144 | 0.001 |
| 15 min after extubation | 75.25 | 2.074 | 104.31 | 5.868 | 0.001 |
| 30 min after extubation | 71.70 | 8.720 | 89.90 | 1.944 | 0.001 |

***Table 2. Comparison of Perioperative Pulse Rate between the Two Groups***

| MAP | Group DS | | Group CS | | P Value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Baseline | 89.45 | 4.499 | 94.45 | 3.901 | 0.902 |
| Pre induction | 95.25 | 5.385 | 99.10 | 1.210 | 0.038 |
| Post induction | 91.00 | 3.878 | 122.15 | 3.951 | 0.001 |
| 1 min after intubation | 90.65 | 5.410 | 118.00 | 3.554 | 0.001 |
| 5 min after intubation | 92.80 | 5.324 | 115.60 | 3.775 | 0.001 |
| Before pneumoperitoneum | 94.60 | 5.540 | 119.95 | 3.017 | 0.001 |
| 5 mins after pneumoperitoneum | 92.40 | 5.093 | 115.70 | 2.296 | 0.001 |
| 10 min after pneumoperitoneum | 91.25 | 5.500 | 111.20 | 1.436 | 0.001 |
| 20 min after pneumoperitoneum | 94.75 | 5.428 | 110.75 | 1.743 | 0.001 |
| 30 min after pneumoperitoneum | 103.00 | 5.437 | 112.80 | 5.167 | 0.001 |
| 45 min after pneumoperitoneum | 93.00 | 2.513 | 126.30 | 2.179 | 0.001 |
| 1 min after extubation | 87.40 | 5.331 | 107.02 | 1.170 | 0.001 |
| 5 min after extubation | 84.35 | 4.135 | 100.90 | 1.212 | 0.001 |
| 15 min after extubation | 89.45 | 3.083 | 99.10 | 1.210 | 0.001 |
| 30 min after extubation | 88.97 | 3.146 | 98.16 | 1.631 | 0.001 |

***Table 3. Comparison of Perioperative Mean Arterial Pressure between the Two Groups***

The pre-operative baseline hemodynamic variables of pulse rate and mean arterial pressure among the two groups were statistically not significant (P value - 0.902) (Table 2 & 3). Compared to control group intramuscular dexmedetomidine group had statistically significant reduction in heart rate, after premedication, preinduction (P – value - 0.001), post induction (P – value - 0.001), 1 minute (P – value - 0.001) and 5 minutes (P – value - 0.001) after intubation (P – value - 0.001), before pneumoperitoneum (P – value - 0.001), 5 min, 10 min, 20 min, 30 min, 45 min, after pneumoperitoneum (P – value - 0.001) and 1 min, 5 min, 15 min, 30 min after extubation (P – value - 0.001) and also 1st hour, 2nd hour, 4th hour in the post-operative period (P – value - 0.001). (Table 2 & 4)

Compared to control group, intramuscular dexmedetomidine group had statistically significant reduction in mean arterial pressure, after premedication, pre induction (P – value < 0.05), post induction (P – value - 0.001), 1 minute (P – value - 0.001) and 5 minutes (P – value - 0.001) after intubation (P – value - 0.001), before pneumoperitoneum (P – value - 0.001), 5 min, 10 min, 20 min, 30 min, 45 min, after pneumoperitoneum (P - value - 0.001) and 1 min, 5 min, 15 min, 30 min after extubation (P - value - 0.001) and also 1st hour, 2nd hour, 4th hour in the post-operative period (P – value - 0.001).(Table 3 & 5)

| Pulse Rate | Group DS | | Group CS | | P Value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Post op 1hour | 75.15 | 1.663 | 86.90 | 1.210 | 0.001 |
| 2 hours | 76.45 | 3.052 | 85.00 | 1.170 | 0.001 |
| 4 hours | 78.70 | 4.669 | 86.90 | 1.483 | 0.001 |

***Table 4. Comparison of Post-Operative Pulse Rate between the Two Groups***

| Mean Arterial Pressure | Group DS | | Group CS | | P - Value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Post op 1 hour | 91.85 | 5.214 | 97.20 | 0.951 | 0.001 |
| 2 hours | 92.30 | 5.079 | 96.85 | 1.424 | 0.001 |
| 4 hours | 92.45 | 5.624 | 96.20 | 0.951 | 0.005 |

***Table 5. Comparison of Post-Operative Mean Arterial Pressure between the Two Groups***

| VAS Score | Group DS | | Group CS | | P - Value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| End of surgery | 1.50 | 0.513 | 4.0 | 0.918 | 0.001 |
| 30 minutes | 3.70 | 1.129 | 5.35 | 1.268 | 0.001 |
| 60 minutes | 5.25 | 0.786 | 7.0 | 1.169 | 0.001 |
| 90 minutes | 6.10 | 1.124 | 6.8 | 0.768 | 0.027 |
| 2 hours | 6.56 | 0.843 | 6.86 | 0.610 | 0.205 |
| 4 hours | 6.72 | 1.104 | 6.75 | 0.842 | 0.923 |

***Table 6. Comparison of Visual Analog Scale between the Two Groups***

The visual analog score between dexmedetomidine group (Group DS) and control group (Group CS) was calculated, and it was found that dexmedetomidine group was statistically significant at the end of surgery, 30 min, 60 min, and 90 min postoperatively (P – value - 0.001).The visual analog score at 2nd hour and 4th hour post operatively was statistically not significant (P value > 0.05).

The frequency of rescue analgesic requirement was significantly higher in group CS. (Table - 6). In group CS, all patients required propofol bolus to control haemodynamics, but in Group DS, only 2 patients required propofol bolus. Four patients in the control group and none in the dexmedetomidine group experienced shivering postoperatively. All patients in group DS had significant dryness of mouth. In group DS, three patients had vomiting postoperatively, in group CS one patient had vomiting.

## DISCUSSION

Dexmedetomidine is an alpha$_2$ - agonist that received FDA (Food and drug administration) approval in 1999. Dexmedetomidine is the dextro isomer of medetomidine. It produces good sedation without respiratory depressant effect. Dexmedetomidine is more selective alpha$_2$ – adrenoceptor agonist than clonidine. It is shorter-acting drug than clonidine. It has an elimination half-life of 2 to 3 hours and highly protein bound > 90 %. Dexmedetomidine is a weak inhibitor of cytochrome p450 enzyme. Because of this effect, when we use dexmedetomidine with opioids, it increases the plasma concentration of opioids. Dexmedetomidine's sedative and cardiovascular effects are effectively reversed by atipamezole which is a selective and specific alpha 2 antagonist.

The mechanism for the sedative effect of dexmedetomidine differs from the sedative effects of drugs which acts on GABA receptors (such as barbiturates, benzodiazepines, propofol). Dexmedetomidine acts on alpha 2 receptors, reduces the sympathetic nervous system outflow and reduces the arousal response. So, the patient will be calm and easily arousable to full conscious state. But the intravenous anaesthetic agents like barbiturates, benzodiazepines, propofol activates the GABA receptors, increase the chloride influx which will produce the hyperpolarisation of post synaptic membrane. It makes the post synaptic membrane more resistant to excitation, results in anxiolysis, sedation, anticonvulsant effect and anterograde amnesia. So, during recovery it produces clouding of consciousness and patient may be in agitated state. It also causes tolerance and dependence. Post operatively, after extubation dexmedetomidine was found to keeps the patients calm and relaxed with no residual ventilatory depressant effect.

When used as premedication in general anaesthesia, dexmedetomidine reduces intubation stress response, reduces intraoperative anaesthetic requirements of inhaled anaesthetics and opioids, reduces the plasma concentrations of stress hormones.

Severe bradycardia and cardiac arrest were reported in a patient receiving intravenous dexmedetomidine infusion while giving general anaesthesia. Benzodiazepines has to be used cautiously with opioids, because it aggravates the ventilatory depressant effect of opioids especially in patients with poor pulmonary reserve. In that situation we can use dexmedetomidine as an alternative for them. It is used in perioperative period as sedative, analgesic, premedication, and as an anaesthetic adjunct for general as well as regional anaesthesia and also for post-operative sedative and analgesia.

So, we used dexmedetomidine, as an adjuvant for premedication since this drug possess sedative, anxiolytic, analgesic and sympatholytic properties with stable hemodynamic profile. It potentiates the anaesthetic effects of all intra-operatively used anaesthetics (intravenous, volatile or regional block). Since bradycardia and cardiac arrest were reported in some patients, receiving intravenous dexmedetomidine infusion, we preferred intramuscular route.

Cengiz kaya et al. found that 1 mcg/kg of intra muscular dexmedetomidine premedication reduced opioid requirement at induction and post-operative period without any changes in hemodynamic parameters.[9] In our study 2 mcg/kg intramuscular dexmedetomidine premedication reduced anaesthetic and analgesic requirement in perioperative period.

Aho, M. scheini et al. compared the effects of three different doses of intramuscular dexmedetomidine (0.6, 1.2, 2.4 mcg/kg) with placebo in patients undergoing gynaecologic diagnostic laparoscopy. They found that maximum MAP and HR after intubation were lower in 2.4 mcg/kg group than placebo group.[10]

M.T. Taittonen et al. studied the effects of clonidine 4 mcg/kg, dexmedetomidine 2.5 mcg/kg intramuscular premedication in elective plastic surgical procedures. They found that dexmedetomidine group had 18 % maximum reduction in HR, 11 % maximum reduction in systolic arterial pressure, and 15 % maximum reduction in diastolic arterial pressure.[11] Aantaa R, et al. compared the effects of Dexmedetomidine 1 mcg/kg intramuscular and inj. midazolam 0.08 mg/kg intramuscular premedication for minor gynaecological surgery. They found that dexmedetomidine group had marked reduction in MAP (20 %) and heart rate (15 %).[12]

Virkkila et al. compared the five different doses of 0.25, 0.5, 0.75, 1.0, 1.5 mcg/kg dexmedetomidine intramuscularly in cataract surgery under regional block. They detected 1 mcg/kg of intramuscular dexmedetomidine produced a 32 % reduction of intra ocular pressure without significant hemodynamic change.[13]

MC Jaakola et al. demonstrated the intubation stress response with intramuscular dexmedetomidine 2.5 mcg/kg and saline placebo intravenously with inj. midazolam 0.08 mg/kg intramuscularly with inj. fentanyl intravenously. They found that hemodynamic changes following intubation was statistically not significant between the two groups.[14]

In our study intramuscular dexmedetomidine premedication 2 mcg/kg reduces the stress response, significant reduction in heart rate, mean arterial pressure during and after intubation, also during extubation, during the pneumoperitoneum and also in the post-operative period.

## CONCLUSIONS

2 mcg/kg of intramuscular dexmedetomidine appears to be an effective premedicant to attenuate the stress induced haemodynamic changes, and is also effective in decreasing the intraoperative anaesthetic and post-operative analgesic requirements and hence it could be a better alternative to other premedicant agents.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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