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# A COMPARATIVE STUDY OF THREE DIFFERENT DOSES OF INTRAVENOUS DEXMEDETOMIDINE INFUSION IN ATTENUATING CIRCULATORY STRESS RESPONSE IN PATIENTS UNDERGOING LAPAROSCOPIC PROCEDURES: A PROSPECTIVE RANDOMIZED CLINICAL TRAIL

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**ABSTRACT** **Background And Aim:** For a successful perianaesthetic effect during laparoscopic procedures there has to be a good control over circulatory stress, sedation and post operative pain relief. Dexmedetomidine is a specific and highly selective alpha-2 adrenergic agonist. It is a beneficial drug to bring down the circulatory stress response of the patients undergoing laparoscopic surgeries. This study is conducted to find out the most appropriate intravenous infusion rate of dexmedetomidine in attenuating circulatory stress response in patients undergoing laparoscopic surgeries.

**METHODS:** Seventy five patients of American society of anaesthesiologist Physical Status I and II undergoing laparoscopic surgeries were categorized into 3 groups, each group having 25 patients. The intravenous dexmedetomidine infusion rate was 0.4 µg/kg/hr in Group A, 0.3 µg/kg/hr in Group B and 0.2 µg/kg/hr in Group C . The IV infusion was started 15 minutes before induction and stopped at the end of surgery. Heart rate (HR), Mean arterial pressure(MAP) and oxygen saturation were measured perioperatively. The results were analyzed using SPSS v 16.0. ANOVA test for continuous variable, post hoc test for intergroup comparison and chi square tests for discrete values were applied.

**RESULTS:** The Circulatory stress response to intubation, creation of pneumoperitoneum, and extubation were reduced in groups A receiving 0.4µg/kg/hr with no significant post-operative adverse effects like bradycardia, hypotension, nausea, vomiting and headache.

**CONCLUSION:** Dexmedetomidine 0.4 µg/kg/hr infusion is the best appropriate dose in attenuating hemodynamic response to intubation, extubation and pneumoperitoneum in laparoscopic surgeries.

**KEYWORDS :** Dexmedetomidine, Laparoscopic Surgeries, Circulatory Stress Response

## INTRODUCTION:

Laparoscopic surgery, is one of the routine surgeries commonly done for abdominal illness and has its own advantages like minimal post-operative pain, reduced hospital stay and better wound healing[1]. In this scenario, like any other surgery, laparoscopic surgery is also linked with stress response produced by the surgery per se and the role of anaesthesia within it. The anesthetic technique for laparoscopic surgery is generally limited to general anesthesia with neuromuscular blockade, tracheal intubation, and mechanical ventilation[2]. Direct laryngoscopy, endotracheal intubation following induction of anesthesia and extubation is associated with hemodynamic changes due to reflex sympathetic system activation caused by epipharyngeal and laryngopharyngeal stimulation. This increased sympatho– adrenal activity may end in hypertension, tachycardia and arrhythmias[1,3].

Pneumoperitoneum during laparoscopic surgery leads to elevated plasma epinephrine, nor-epinephrine levels and higher renin activity. These effects cause increase in heart rate, blood pressure, systemic and pulmonary vascular resistance, and reduced cardiac output[4,5]. Many drugs are used to attenuate the intubation and extubation response such as esmolol, intravenous lignocaine, fentanyl, remifentanil, labetalol, local anaesthesia blocks, dexmedetomidine and nebulization with many drugs like lignocaine, fentanyl, etc[6–9].

There is an uncertainity about the rate of intravenous infusion of dexmedetomidine that will be appropriate in attenuating the rise in the sympatho adrenal activity during intubation, extubation and creation of pneumoperitoneum.

We therefore conducted this prospective, randomized trial to compare the three different doses of dexmedetomidine intravenous infusion and to find out the most appropriate intravenous infusion rate in attenuating circulatory stress response in patients undergoing laparoscopic procedures.

## MATERIAL AND METHODS:

After getting approval from the institutional Ethical Committee, this prospective, randomized, parallel-group, double blinded, the clinical trial study was conducted in Sri Lakshmi Narayana Institute of Medical sciences. Seventy-five patients of ASA physical grading of I and II, aged between 20 to 60 years of both gender who were planned for laparoscopic surgeries like appendectomy, cholecystectomy, and diagnostic laparoscopy in gynecology were selected for the study. The patients with ASA III and above, diabetes, heart disease, hypertension, and pregnant women, were excluded. The patients were excluded if BMI is more than 30, anticipated difficult intubation, patients on any chronic medications and the time of pneumoperitoneum exceeds beyond 1 hour. All the patients were enrolled after obtaining written informed consent and after a thorough pre-anesthetic checkup including general, physical, and systemic examinations, and airway assessment was done by Mallampati grading. Randomization was performed by computer-generated random numbers and allocation concealment was done by prefilled numbered syringes. This was done by a separate anesthesiologist who was not aware of the study protocol and was not involved in administering drugs or data collection during the study. The patients were not aware of the group allocated to them.

In the operating room, an IV line was secured with an 18-G venous cannula and Ringer's lactate infusion (6 ml/kg) was started. Routine standard monitors such as pulse oxymetry, electrocardiography (ECG), and non-invasive blood pressure were attached and monitoring started. Patients were premedicated with glycopyrrolate 0.2 mg IV and fentanyl 2 µg/kg IV. In all patients, dexmedetomidine infusion was started 15 minutes before induction. The intravenous dexmedetomidine infusion rate was 0.4 µg/kg/hr in Group A, 0.3 µg/kg/hr in Group B and 0.2 µg/kg/hr in Group C.

The patients were pre oxygenated with 100 % O2 for 3 mins. The induction was done with Inj. Propofol 2 mg/kg iv followed by Inj. Succinylcholine 2mg/kg iv. Direct laryngoscopy was attempted 30 s after the administration of succinylcholine with Macintosh curved blade number 3 by an anesthesiologist having more than 5 years of experience. The trachea was intubated with an appropriate-sized, cuffed disposable ET tube. When laryngoscopy and intubation duration exceeded 20 seconds, those patients were excluded from this study. After intubation, mechanical ventilation started and patients were connected to a circle system to keep the EtCO2 between 35 and 45 mm Hg. Anaesthesia was maintained with O2:N2O mixture, isoflurane(0.5% – 1%), and injection Atracurium 0.5mg/kg iv was used to maintain the neuromuscular blockade. Laparoscopy was done by standard surgical technique and pneumoperitoneum was created with non humidified carbon dioxide (CO2) at an intraabdominal pressure between 12 and 14 mm Hg. At the end of the surgery, all patients were reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.008 mg/kg IV. Patients were extubated with effective oral suctioning after adequate recovery and then shifted to the anesthesia recovery room.

Patients hemodynamic variables such as Heart Rate (HR), Mean Arterial Pressure (MAP) were recorded at baseline, 15 min after starting the dexmedetomidine infusion, 1 minute after intubation, 5 min after intubation, 1 minute after the creation of pneumoperitoneum, thereafter every 10 minutes. Monitoring was continued after extubation at 1 minute, 5 min, 15 min, 30 min, and 60 minutes intervals. In the PACU room, patients were observed for adverse effects like bradycardia, rebound hypertension, nausea, vomiting, and headache. In the recovery room, the patient's recovery from anaesthesia was assessed according to the Modified Aldrete Scoring system (ASS). The hemodynamic alterations like a decrease in MAP greater than 20% below the baseline value or SAP less than 90 mm of Hg were treated primarily by increasing the iv fluid infusion rate and then reducing isoflurane concentration or incremental doses of ephedrine 4 mg bolus IV. Heart rate less than <50/min was treated with atropine 0.6 mg IV. The Anesthetist and staff nurse in the post-anesthesia care unit were unaware of the study treatment protocol to which each patient was randomized. All the hemodynamic data were recorded by an independent observer who was blinded to the study solution.

**Statistical Analysis:**

Collected data were analyzed using appropriate descriptive and inferential statistics using SPSS 16.0-Software. Normally distributed interval and ratio data were analyzed using the ANOVA test. Categorical data were analyzed using Chi-square or Fischer Exact whichever is appropriate. Data were analyzed for statistical significance of p-value <0.05. If the difference was found to be significant, further intergroup analyses were carried out.

## RESULTS:

We found that the demographic parameters were comparable among the three groups (*P* >0.05) [Table 1]. There was no significant difference in the baseline patient's characteristics and baseline preoperative variables among the three groups. All 75 patients completed the study. Duration of pneumoperitoneum in all the patients was less than 60 min and there was no statistically significant difference among the three groups (p>0.05). Ratio or interval data are expressed as mean ±SD and ASA I/ II, Gender and the type of laparoscopic procedures were expressed as numbers**.**

**Table 1: Patients Characteristics And Demographic Parameters**

| Variable | Group A (n=25) | Group B (n=25) | Group C (n=25) | P value |
|---|---|---|---|---|
| ASA I/II (n) | 20/5 | 22/3 | 21/4 | >0.05 |
| Gender (Male/Female) | 18/7 | 16/9 | 19/6 | >0.05 |
| Appendectomy/Cholecystectomy/diagnosic laparoscopy | 11/6/8 | 11/7/7 | 12/7/6 | >0.05 |
| Age ( years) | 35.8 ± 8.6 | 31.3 ±6.5 | 33.5 ± 9.3 | >0.05 |
| Weight(kg) | 70.2 ± 5.3 | 68.6 ±6.1 | 73.4 ± 5.0 | >0.05 |
| Height (m) | 1.64 ± 0.06 | 1.60 ±0.06 | 1.62 ±0.07 | >0.05 |
| Duration of pneumoperitonium | 40 ±4.6 | 43 ±5.8 | 42 ±4.8 | >0.05 |

Hemodynamic variables recorded in three groups at specified intervals are shown in [Figure 1], [Table 2]. There was no significant difference in baseline HR and MAP among the three groups (p>0.05). After 15 minutes of dexmedetomidine infusion, the heart rate was 78.28±10.2 in Group A, in Group B 86.44±12.88, in Group C 92.04±10.87. This difference was statistically significant (p<0.05). Mean arterial pressure after 15 minutes of dexmedetomidine infusion was 88.15±4.5 mmHg in Group A, in Group B 94.14±6.3 mmHg, in Group C 97.8±7.7mmHg. This difference was statistically significant (p<0.05). Group A had lower HR and MAP than both Group B and Group C which was statistically significant (p<0.05).

Heart rate and Mean arterial pressure were significantly lower in group A at 1 min after tracheal intubation, 1 min after creation of pneumoperitonium and at 1 min after extubation, compared to group B and Group C (*P* < 0.01). Both Group B and Group C had higher HR and MAP when compared to Group A throughout the study period.

**Table2 Heart Rate In All Groups**

| | Group A | Group B | Group C | |
|---|---|---|---|---|
| Baseline | 89.46±9.4 | 90.3±10.73 | 88.78±10.75 | p>0.05 |
| 15 min after dex infusion | 78.28±10.2 | 86.44±12.88 | 92.04±10.87 | P<0.05 |
| 1 min after intubation | 78.42±12.82 | 106.18±11.65 | 110±13.56 | P<0.05 |
| 5 min after intubation | 73.86±10.5 | 98.28±12.78 | 108±12.65 | P<0.05 |
| 1min after pp | 79.86±9.92 | 106.39±11.65 | 113.48±10.43 | P<0.05 |
| 5 min after pp | 76.78±11.32 | 100.08±10.78 | 106.4±11.06 | P<0.05 |
| 10 min after pp | 75.68±10.86 | 98.68±11.21 | 102.7±10.45 | P<0.05 |
| 20 min after pp | 77.56±10.34 | 94.8±12.76 | 101.7±11.67 | P<0.05 |
| 30 min after pp | 76.88±11.24 | 89.46±11.86 | 99.62±10.43 | P<0.05 |
| 40 min after pp | 77.98±11.23 | 88.06±13.42 | 96.92±13.20 | P<0.05 |
| at the time of extubation | 81.69±12.64 | 96.18±10.68 | 111.62±10.34 | P<0.05 |
| 5 min after extubation | 78.62±11.78 | 90.28±11.28 | 108.12±10.6 | P<0.05 |
| 15 min after extubation | 74.5±11.0 | 86.62±11.86 | 99.55±11.33 | P<0.05 |
| 30 min after extubation | 73.6±11.87 | 80.46±12.66 | 96.4±9.30 | P<0.05 |
| 1 hr after extubation | 70.44±10.44 | 80.4±10.4 | 88.44±10.73 | P<0.05 |

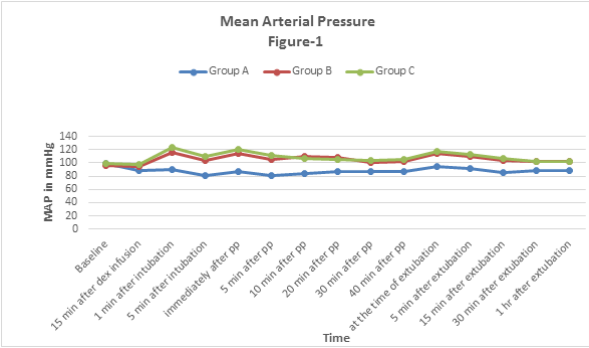


**Table- 3 Side Effects**

| Side effects | Group A | Group B | Group C | P value |
|---|---|---|---|---|
| Nausea/Vomiting | 1 | 1 | 2 | >0.05 |
| Bradycardia | 0 | 0 | 0 | >0.05 |
| Hypotension | 0 | 0 | 0 | >0.05 |
| Headache | 0 | 0 | 0 | >0.05 |

The Modified Alderete Score was more than 8 in the patients of all the three groups. There was no statistically significant difference in the incidence of nausea and vomiting among the three groups (p>0.05).

## DISCUSSION:

Dexmedetomidine, a highly selective and potent alpha2-adrenergic agonist, has a potentially useful role as an anxiolytic, sympatholytic, sedative, and analgesic agent in routine anaesthesiology and critical care practice. So it can be a useful adjunct for premedication, especially for patients susceptible to preoperative and perioperative stress[10]. Dexmedetomidine was approved by the Food and Drug Administration at the end of 1999 for use in humans as a short-term medication (<24 hours) for analgesia and sedation in the intensive care unit (ICU)[11]. Its unique properties render it suitable for sedation and analgesia during the whole perioperative period. It is used as a premedication, as an anesthetic adjunct for general and regional anesthesia, and it is also used for the postoperative sedative and analgesic purposes[12]. The adverse effects of dexmedetomidine mostly due to cardiovascular depression include hypotension, bradycardia, and arrhythmias. The incidence of postoperative bradycardia has been reported as high as 40% in healthy surgical patients who received dexmedetomidine, especially high doses[13].

Endotracheal intubation and extubation are associated with significant sympathoadrenal response and cause increases in heart rate, arterial pressure, and plasma catecholamine concentrations. Dexmedetomidine attenuated this sympathoadrenal activation during tracheal intubation effectively but did not completely abolish the cardiovascular response[14]. In particular, dexmedetomidine can provide a dose-dependent cooperative sedation that allows ready interaction with the patient. Dexmedetomidine increases the hemodynamic stability by altering the stress-induced sympathoadrenal responses to intubation during surgery and emergence from anesthesia[12].

Scheinin et al.,[14] found the effect of intramuscular dexmedetomidine

on tracheal intubation, induction dose, and preoperative analgesic requirements. They concluded that dexmedetomidine attenuated the hemodynamic responses to intubation in laparoscopic gynecological surgeries. The concentration of noradrenaline in mixed venous plasma was lower in the dexmedetomidine group. Lawrence et al.,[15] studied that a single dose of 2 mcg/kg of dexmedetomidine before induction of anesthesia attenuated the hemodynamic response to intubation as well as that to extubation. Bradycardia was observed at the 1st and 5th min after administration. This might have been due to bolus administration. In our study we used three infusion rates, namely 0.4 mcg/kg/hr, 0.3 mcg/kg/hr and 0.2 mcg/kg/hr. Hemodynamic stability was better in the dexmedetomidine in 0.4 mcg/kg/hr (group A) and none of the patients had developed bradycardia in our study. Manne et al.,[16] found that 0.4 mcg/kg/hr dexmedetomidine infusion reduced the stress response in laparoscopic cholecystectomy surgeries. Our study results also concluded that 0.4 mcg/kg/hr dexmedetomidine was the most effective intravenous infusion rate to attenuate the increase in heart rate and blood pressure compared to lower infusion rates (Group B and C). This finding supports and correlates to our study.

Masoori et al.,[17] demonstrated that dexmedetomidine infusion was effective for attenuating the hemodynamic changes due to laryngoscopy and laparoscopy but was better with maintenance infusion of dexmedetomidine in a dose of 0.6 µg/kg/hr than 0.3 µg/kg/hr. Similarly, in our study, 0.3 µg/kg/hr infusion of dexmedetomidine was not as effective in attenuating the stress response to tracheal intubation and extubation. Our study was similar to the study by rani *et al.*,[18] who demonstrated that bolus dose of 0.75 mcg/kg dexmedetomidine given 15 min before extubation provided better extubation quality. In our study also MAP and Heart rate after extubation in the patients receiving 0.4 µg/kg/hr was significantly lower as compared to lower intravenous infusion rates.

The α-adrenoceptors are involved in regulating the autonomic nervous system and cardiovascular systems. Dexmedetomidine stimulates presynaptic α2-adrenoceptors, thus inhibiting the release of norepinephrine and hence the propagation of pain signals. It also works postsynaptically to produce a decrease in blood pressure and heart rate[19]. α2 -adrenoceptors are also located within the central nervous system and their activation leads to sedation, a reduction of tonic levels of sympathetic outflow, and an augmentation of vagal activity. The use of α2 -agonists in the peri-operative period has been associated with reduced anesthetic requirements and attenuated heart rate and blood pressure responses to stressful events[10,12].

The limitation of this study is that plasma norepinephrine level was not measured.

## CONCLUSION:

Dexmedetomidine 0.4 µg/kg/hr infusion is the best appropriate dose in attenuating hemodynamic response to intubation, extubation, and pneumoperitoneum in laparoscopic surgeries with minimal side effects.

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