

## Dexmedetomidine as an adjunct in laparoscopic surgery along with entropy as a tool to measure the anaesthetic depth

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**Introduction:** Dexmedetomidine is a drug that can be used for various anaesthetic indications such as an adjuvant for general anaesthesia and regional blocks, in premedication, as a hypnotic and analgesic postoperatively.

**Aim:** To study the effect of dexmedetomidine as an adjuvant in anaesthesia for laparoscopic surgery using entropy as an instrument to monitor the anaesthetic depth.

**Methods and materials:** Sixty patients were enrolled for the study, thirty receiving dexmedetomidine infusion (group 1) and thirty receiving saline infusion (group 2). Prior to induction, an entropy sensor was positioned as per manufacturer's recommendation. Patients received a loading dose of given drug, either dexmedetomidine or saline, followed by an infusion for maintenance. All patients were given general anaesthesia with propofol and fentanyl. The given drug infusion was continued until extubation.

**Results:** Mean systolic and diastolic blood pressure during extubation showed 5% and 8.5% increase respectively from baseline in the dexmedetomidine group ( $p > 0.050$ ) as compared to 19% and 15% increase respectively in the saline group which was significant ( $p < 0.05$ ). The dose of propofol used was reduced significantly; mean dose requirement for induction was  $59 \pm 22.07$  in group 1 as compared to  $97.74 \pm 27.044$  in group 2. There was marked reduction in the opioid requirement intraoperatively in group 1 ( $21.66 \pm 27.64$ ) as compared to group 2 ( $41.613 \pm 28.384$ ) with adequate depth of anaesthesia (DOA) maintained.

**Conclusion:** Dexmedetomidine is an effectual anaesthetic adjunct that can be used in laparoscopic surgeries with an excellent recovery profile and provides adequate depth of anaesthesia.

**Keywords :** depth of anaesthesia; propofol; opioid; entropy; monitor; dexmedetomidine

### Introduction

Anaesthesiologists require to provide adequate depth of anaesthesia (DOA) in laparoscopic surgeries because these surgeries most particularly are associated with increased blood pressure (BP) and systemic vascular resistance.<sup>1</sup> Dexmedetomidine has wide applications in anaesthesia.

It can be used for effective premedication, attenuation of the laryngoscopic response and prevention of emergence delirium.<sup>2</sup> It also provides superior analgesia after surgery and decrease in opioid requirements.<sup>3,4</sup> It has minimum alveolar concentration (MAC) sparing properties<sup>5</sup>, decreases the incidence of postoperative nausea and vomiting (PONV), reduces metabolic demand of oxygen postoperatively which is helpful in cardiac patients and attenuates post-operative shivering.<sup>6</sup>

The sedative properties of dexmedetomidine is from the site of action in locus ceruleus.<sup>7,8</sup> Its sympatholytic effect which results in hypotension and bradycardia is mainly due to the activation of post-synaptic  $\alpha_2$  receptors, thus reducing the release of catecholamines.<sup>9</sup>

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In this study, dexmedetomidine in laparoscopic surgeries and its effects on haemodynamic response, analgesic and anaesthetic requirement was observed. To prevent under dosing of anaesthetic drugs causing awareness under anaesthesia entropy was included as a monitoring tool.

The entropy monitor generates two indices, one reflects the cortical activity, the state entropy (SE), and the response entropy (RE) includes frontal electromyography (EMG) activity.<sup>10</sup> When patient is responding to an external stimulus like pain an EMG signal suddenly appears<sup>11</sup> which alerts the anaesthesiologist to deepen the DOA. Normalizing both SE and RE is advantageous because when EMG power becomes zero SE will be the same as RE. RE ranges from zero to hundred and SE from zero to ninety-one. Lower values (40-60) indicate deeper levels of depth of anaesthesia.<sup>12,13</sup>

Our objectives were to determine

1. Whether dexmedetomidine would be an effective adjunct with respect to decrease in the anaesthetic requirements?
2. To assess effect of dexmedetomidine on the haemodynamics.
3. Does dexmedetomidine have propofol and opioid sparing action (depth maintained with entropy)?

### Methods and Materials

This was a prospective cohort observational study conducted in hospitals of Kasturba Medical College. Study duration was from September 2012 to August 2014. After Institutional Ethics Committee (IEC) approval, 60 patients of American Society of Anaesthesiologists (ASA) grade I and II, between 18 to 60 years of age, posted for surgery under general anaesthesia were enrolled. 30 patients in each group was the required sample size calculated at a power of 90% and a confidence level of 95% based on a previously published data.<sup>1</sup> Laparoscopic surgeries included cholecystectomy, appendicectomy and laparoscopic adhesiolysis. Exclusion criteria was patient

refusal, III/IV ASA grade, any contraindication to the use of dexmedetomidine e.g. bradycardia, hypotension, ventricular dysfunction, cardiac failure, heart blocks, renal or liver disorder, history of head injury, patients with neurologic disorders, substance abuse, patients on anticholinergic, clonidine medications and any scalp or skull deformities. A valid written informed consent was obtained from patients posted for laparoscopic surgery under general anaesthesia. The infusion of the given drug was prepared in normal saline. Dexmedetomidine group (Group 1) in the concentration of 4µg/ml and the other was with plain normal saline (Group 2). Groups were allotted by the sealed envelope technique. Baseline monitors like non-invasive blood pressure (NIBP), oxygen saturation (SpO<sub>2</sub>), electrocardiogram (ECG) and entropy were attached. As recommended by the manufacturer, the forehead was wiped with spirit and an Entropy Sensor (Entropy Sensor, GE Healthcare) was attached. While the patient was awake the bio signal from the patient's forehead was recorded. Before induction, the impedance was noted and a value below 7.5k was acceptable. The pre-induction values of RE and SE, pulse oximetry, heart rate (HR) and blood pressure (BP) were noted. Loading dose of either dexmedetomidine or saline of 1µg/kg infusion was given over 15 minutes and then maintained at 0.2µg/kg/h. All patients were given general anaesthesia with premedicants midazolam 0.02mg/kg and 1.5µg/kg fentanyl intravenously. Induction was done with 5mg IV titrated doses of propofol until the entropy value of 40-60 was reached. 1mg/kg i.v. rocuronium was used as muscle relaxant. Haemodynamic response to direct laryngoscopy and endotracheal intubation was noted. Oral intubation was done, and placement confirmed with bilateral equal air entry and end-tidal carbon dioxide (EtCO<sub>2</sub>) trace. Anaesthesia was maintained with oxygen, nitrous oxide (N<sub>2</sub>O) mixture (60:40), and sevoflurane to attain MAC of 1 and vecuronium top ups was used as muscle

relaxant. Intraoperative anaesthetic requirement was gauged by HR and BP, end point for requirement for both was considered a 20% increase from baseline value, and SE value, while the analgesic requirement was titrated with RE, with an aim to maintain both RE and SE around 40-60. Whenever required, propofol 10mg boluses were given to deepen the plane of anaesthesia. Analgesia was repeated according to RE in the form of fentanyl top ups of 10µg. The given drug infusions were continued until extubation. Neuromuscular relaxant was reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.01mg/kg. Extubation response with respect to HR and BP was documented. At the end of surgery, paracetamol 1g i.v. was given for postoperative analgesia. Any adverse effects like bradycardia, hypotension, PONV and respiratory depression were noted. After two hours of observation in the recovery room, patients were shifted to the ward.

**Statistical analysis**

30 patients in each group was the required sample size calculated at a power of 90% and a confidence level of 95% based on a previously published data.<sup>1</sup> Statistical package for the Social Sciences (SPSS) 17 (SPSS Inc., Chicago, Illinois, USA) was used to do the analysis. Chi-square test was used for parametric values. Students unpaired ‘t’ test was used to determine a statistical difference between the groups. In the above tests, the ‘p’ value of less than 0.05 was indicative of statistical significance.

**Results**

The difference of proportions of subjects observed between the study groups with respect to ASA physical status, age, weight, BMI and sex was comparable. (Table 1, 2, 3)

**Table 1:** Age, weight and BMI distribution in each group

Group	N	Mean Age (in years)	Weight (in kgs)	BMI
Group1	30	38.01±10.92	61.63±11.97	24.83±4.81
Group2	31	35.517±10.64	57.22±13.10	24.35±4.90
P value		P=0.372	P=0.176	P=0.706

Values expressed as mean ± SD

**Table 2:** Sex distribution in each group

	Group1	Group2	Total
Female count %	22 73.3%	25 80.6%	47 77%
Male count%	8 26.7%	6 19.4%	14 23%
Total count%	30 100%	31 100%	61 100%

Chi square value= 0.461, df-1, p value- 0.497

**Table 3:** ASA distribution in each group

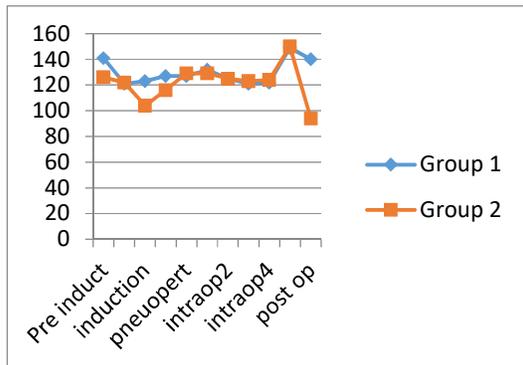
	Group1	Group2	Total
ASA I count %	14 46.7%	18 58.1%	32 52.4%
ASAII count %	16 53.3%	13 41.9%	29 47.5%
Total count %	30 100%	31 100%	61 100%

**Table 4:** Requirement of anaesthetic agents

	group	N	Mean± SD	P value
Induction – propofol	Group1	30	59.00±22.03	
	Group2	31	97.74±27.04	<0.001
NMB rocuronium	Group1	30	53.00±10.22	
	Group2	31	50.80±9.32	=0.384
NMB vecuronium	Group1	28	1.57±1.93	
	Group2	29	1.20±1.78	=0.462
Maintenance—propofol	Group1	30	36.80±46.08	
	Group2	31	53.83±41.09	=0.133
Fentanyl top up	Group1	30	21.66±27.64	
	Group2	31	41.61±23.38	=0.007

The mean induction dose requirement of propofol was  $59 \pm 22.07$  in group 1 as compared to  $97.74 \pm 27.044$  in group 2. The dose of propofol intraoperatively for adequate anaesthetic depth was also decreased in group 1 as compared to group 2 with statistical significance. There was marked reduction in the opioid requirements intraoperatively in group 1 ( $21.66 \pm 27.64$ ) as compared to group 2 ( $41.613 \pm 28.384$ ). The difference of proportions of subjects observed between the two groups with respect to neuromuscular agent, vecuronium, used was not statistically significant. ( $t = 0.741, p = 0.462$ ) (Table 4)

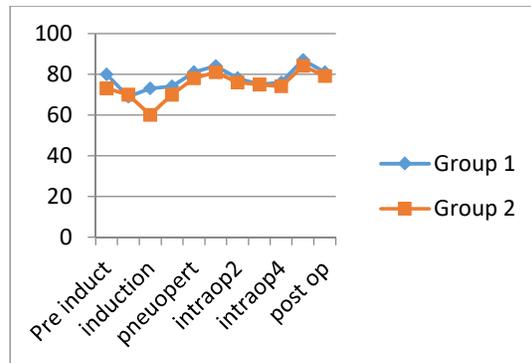
**Figure 1:** Systolic blood pressure variability of two groups at different time periods



The mean blood pressure at start was elevated in group 1 than group 2. There was 14% reduction in the mean systolic blood pressure after loading dose of dexmedetomidine which was highly significant as compared to 3% reduction in the saline group. After that minimal change was observed for entire duration of infusion. Mean systolic BP at intubation, at creation of pneumoperitoneum, every 15 min intraoperatively, at extubation and post extubation in group 1 was found to be  $127.27 \pm 25.388, 127 \pm 25.4, 132 \pm 23.403, 149.90 \pm 14.430, 140.10 \pm 16.875$  respectively whereas that of group 2 at same time intervals was  $116.740 \pm 20.115, 129.23 \pm 23.40, 129.74 \pm 21.407, 150.65 \pm 25.292, 133.06 \pm 16.63$ , respectively and the difference was not found to be statistically significant ( $p > 0.050$ ). There was good control of systolic blood pressure during

laryngoscopy, with minimal or no change in systolic blood pressure with pneumoperitoneum in both the groups. Mean systolic blood pressure during extubation increased from  $141.70 \pm 20.84$  to  $149.90 \pm 14.430$  i.e. 5% increase in the dexmedetomidine group from the baseline which was not significant  $p > 0.050$  as compared to 19% increase in the saline group i.e. from  $126 \pm 20.77$  to  $150.65 \pm 25.292$  which was highly significant  $p < 0.050$ . (Figure 1)

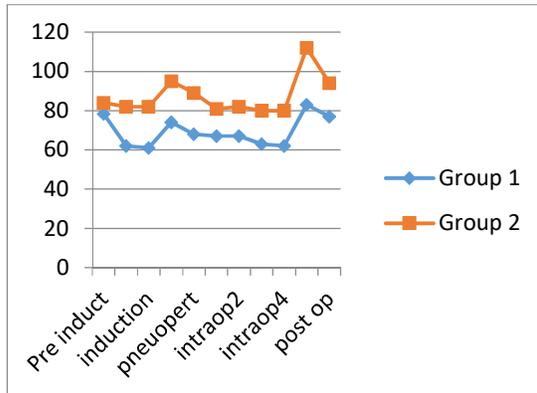
**Figure 2:** Diastolic blood pressure variability of two groups at different time periods



The mean diastolic blood pressure at start was higher in group 1 ( $80.7 \pm 10.07$ ) as compared to group 2 ( $73.19 \pm 11.38$ ). There was 14.4% reduction in the mean diastolic blood pressure after loading dose of dexmedetomidine which was highly significant as compared to 3.7% reduction in the saline group. After that minimal change was observed for entire duration of infusion. Mean diastolic blood pressure at intubation, at creation of pneumoperitoneum, every 15 min intraoperatively, at extubation and post extubation in group 1 was found to be  $74.07 \pm 15.909, 81.27 \pm 16.758, 84.13 \pm 15.462, 87.57 \pm 9.863, 81.87 \pm 10.559$  respectively whereas that of group 2 at same time intervals was  $70.13 \pm 11.427, 78.06 \pm 13.434, 81.03 \pm 12.582, 84.48 \pm 14.980, 79.23 \pm 10.379$ , respectively and the difference was not found to be statistically significant ( $p > 0.050$ ). Mean diastolic blood pressure during extubation increased from  $80.70 \pm 10.07$  to  $87.57 \pm 9.86$  i.e. 8.5% increase in the

dexmedetomidine group which was not statistically significant as compared to 15% increase in the saline group i.e. from  $73.19 \pm 11.38$  to  $84.48 \pm 14.980$  which was statistically significant  $p < 0.050$ . (Figure 2)

**Figure 3:** Heart rate variability of two groups at different time periods



Mean HR on starting was  $78.27 \pm 11.03$  which fell to  $62.07 \pm 13.50$ ;  $p < 0.001$  i.e. 20% reduction in the Group 1 in comparison to 1.6% reduction Group 2. There was a fall in HR at beginning in Group 1. Mean heart rate at intubation, at creation of pneumoperitoneum, every 15 min intraoperatively, at extubation and post extubation was found to be  $p < 0.050$  between groups 1 and 2. There was good control of HR during laryngoscopy, with minimal or no change with pneumoperitoneum and during extubation in the group 1 while increase in the mean HR during intubation and extubation was noted in Group 2. (Figure 3)

### Discussion

As already known, dexmedetomidine potentiates anaesthetic effects of all intraoperative anaesthetics. It causes profound reduction in anaesthetic requirement as shown to be mediated through central  $\alpha_2$  adrenergic receptors. A study conducted in 2012 by Poonam S Ghodki et al<sup>1</sup> observed a 62.5% decrease in the propofol induction dose with the use of dexmedetomidine. Findings are similar in this study in which we observed a 39.6%

induction dose reduction of propofol in the dexmedetomidine group. We also observed a reduction in the intra operative requirements of propofol to maintain adequate depth of anaesthesia i.e. entropy between 40-60 i.e. from  $36.80 \pm 46.08$  in the dexmedetomidine group as compared to  $53.83 \pm 41.07$  in saline group showing no statistical significance. Anne Vakkuri et al<sup>12</sup> found that during the entire anaesthesia period, propofol usage was lesser in the group where entropy was monitored particularly in the last 15 min. ( $p < 0.001$ )

Ghodki et al study also showed reduced requirement of inhalation that is isoflurane (25%-35%) reduction, however, in this study we kept MAC at 1 maintaining dial concentration of sevoflurane between 1-2% constant for both the groups.

Studies done<sup>14,15</sup> on how dexmedetomidine blunts the vasopressor response to tracheal intubation and anaesthetic requirement perioperatively, observed that there was significant anaesthetic and opioid sparing effect. In our study there was good control of systolic and diastolic blood pressures during laryngoscopy, with minimal or no change in blood pressures with pneumoperitoneum in both the groups. However, mean SBP during extubation showed a 5% elevation in the group dexmedetomidine from the baseline to a 19% increase in the saline group. Mean DBP during extubation showed an 8.5% increase in the dexmedetomidine group when compared to 15% increase in the saline group There was good control of HR during laryngoscopy, with minimal or no change with pneumoperitoneum and extubation in the dexmedetomidine group but there was a substantial increase in the mean HR during intubation and extubation in the saline group. In the saline group the pressor response was attenuated by giving additional top up of propofol and fentanyl to deepen the plane of anaesthesia. Hence opioid requirement intraoperatively was much higher in the saline group than in the dexmedetomidine group i.e. there was about 49% increase in the

requirement of fentanyl with respect to the dexmedetomidine group. ( $p=0.007$ )

Respiratory depression is much less with dexmedetomidine than other sedatives and due to this property, dexmedetomidine infusion can be continued safely through extubation while other sedative agents often necessitate their stoppage during extubation period.<sup>8</sup> However, in our study, no episodes of respiratory depression was seen in any patients in the post-operative period. The difference of proportions of subjects observed between the two groups with respect to SpO<sub>2</sub>, respiratory rate and EtCO<sub>2</sub> was not statistically significant, at the starting of the surgery, and also intra operatively ( $p>0.05$ ).

Dexmedetomidine is shown to have a better recovery profile. On awakening, patients return to their initial level of consciousness.<sup>16</sup> Our results suggest that the entropy monitor reliably indicates the level of dexmedetomidine-induced sedation although it produces hypnosis similar to physiological sleep. This was substantiated by Hall *et al.*<sup>4</sup> using bispectral index (BIS) monitoring system and psychometric tests.

### Conclusion

From this study we conferred that dexmedetomidine can be used as an anaesthetic adjuvant which decreases the requirement of anaesthetics and opioids as seen by the decrease in the dose of propofol and fentanyl used during the surgery. We also conclude that dexmedetomidine attenuates sympathoadrenal response and maintains desirable haemodynamics. Using entropy helped maintain effective anaesthetic depth with an excellent recovery profile.

### Limitations of the Study

This study was limited to a small population included in two medical academic centres. We did not study the effect of dexmedetomidine on inhalational requirement and we kept MAC constant for both the groups. Monitoring depth of

anaesthesia only may result in under dosing analgesic requirement and further studies are required to substantiate these findings.

Haemodynamic disturbances in laparoscopic surgery are multifactorial. After induction of anaesthesia it could be due to surgical stimulation, peritoneal stretching, effects of pneumoperitoneum and increase abdominal pressures, patient positioning and hypercarbia among other reasons. Depth of anaesthesia monitoring is used to prevent accidental awareness.

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