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Original Research Article

Search for an Ideal Anaesthetic Adjuvant in Laparoscopic Surgeries: Does Dexmedetomidine Fit In? A Randomized Control Trial

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Abstract: ***Background and Aim*:** Dexmedetomidine, a selective alpha-2 adrenergic agonist, has been used to blunt various stress responses during general anaesthesia including that of pneumoperitoneum. It also has synergistic effects when used as an adjuvant with anaesthetic agents. Our study aimed to assess the efficacy of dexmedetomidine without any initial bolus at an infusion dose of 0.5 mcg/kg/hour, in attenuating the haemodynamic stress response to pneumoperitoneum in laparoscopic surgeries and evaluate the efficacy of its synergistic effects at this dose. ***Methods*:** 60 American Society of Anaesthesiologists physical status I/II patients, 18-60 years, undergoing elective laparoscopic surgery were randomized into 2 groups: Group I received dexmedetomidine and group II normal saline @ 0.5 mcg/kg/hour intravenously, started before premedication till the end of pneumoperitoneum. Heart rate and blood-pressure were monitored continuously. Anaesthetic agents and analgesics were titrated to maintain entropy of 40-60. ***Results*:** Compared to group II, group I showed significant blunting of HR and BP rise during entire duration of pneumoperitoneum ($p<0.05$). There was reduced requirement for propofol, fentanyl and isoflurane, showing significant MAC sparing effect ($p<0.0001$) in group I vs group II. Patients in group I also exhibited earlier emergence, without residual sedation ($p<0.0001$). ***Conclusion*:** Without any initial bolus, Dexmedetomidine infusion @0.5 mcg/kg/hour, when started timely before induction of pneumoperitoneum, effectively attenuated the hemodynamic stress response to pneumoperitoneum, significantly reduced anaesthetic/analgesic requirements exhibiting good synergistic effect, while maintaining depth of anaesthesia, resulting in early and smooth emergence. This dose achieves maximum efficacy with minimal side effects.

Keywords: Dexmedetomidine, Adjuvant, Pneumoperitoneum, Hemodynamic Stress Response, Entropy, MAC Sparing Effect

Trial Registration: CTRI/2023/07/055718.

INTRODUCTION

Laparoscopic surgery has become popular due to its advantages including minimal scarring, less postoperative pain and shorter hospital stay [1, 2]. Despite all these benefits, there are some key hemodynamics concerns from an anesthetist's perspective due to creation of CO2 pneumoperitoneum causing elevated intraabdominal pressure that leads to inferior vena cava compression, reduced venous return and later on increased systemic vascular resistance and mean arterial pressure which are of concern particularly in patients with pre-existing cardiovascular conditions [1, 2].

Traditional approaches for managing these effects involve optimizing preoperative fluid status, minimizing extreme patient positioning [3], decreasing pneumoperitoneum pressure, increasing depth of anaesthesia even when the patient is not in lighter plane of anesthesia but for the sake of decreasing BP, using multiple pharmacological agents such as esmolol, nitroglycerine, magnesium sulphate, even clonidine in some cases to tackle these haemodynamic changes due to mechanical and neurohumoral factors causing increase in catecholamines, and vasopressin levels [2- 8].

Clonidine, an alpha2-adrenergic agonist has already been studied to effectively attenuate this haemodynamic stress response to pneumoperitoneum [4-9].

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For the last few years, a newer drug of this family, dexmedetomidine, which is 16 times more specific with better safety profile is gaining popularity as an important drug in anesthesia armamentarium, now being used through different routes like oral for premedication, iv for ICU sedation, procedural sedation , as an adjuvant during GA, in peripheral nerve blocks [10], and in epidural [10], both to potentiate intraoperative anesthesia and prolong post-operative analgesia, every time proving to be of adding benefits to the patient while they are going through acute stressful period of surgery. Its distinct properties of sympatholysis, sedation, and analgesia make it an effective anaesthetic adjuvant [11, 12].

However, a wide variation in the i.v. dose of dexmedetomidine has been found in previous studies that have used it to manage haemodynamic changes in laparoscopic surgeries, with most of them using an initial bolus of 0.5 or 1.0 mcg/kg followed by infusion varying from 0.2 to 0.6mcg/kg/hour; some as single bolus only and others as a continuous infusion only with comparison of different infusion rates varying from 0.4 to 0.8 mcg/kg/hour [5-16]. Moreover, most of the previous studies have highlighted only the sympatholytic action of dexmedetomidine leading to attenuation of hemodynamic stress response [5-18], except a few [13-19], that have mentioned other potential benefits of dexmedetomidine leading to an overall more balanced and appropriate anaesthetic care during laparoscopic surgeries [11-13]. One study by Ghodki PS *et al*., [13], has mentioned that with dexmedetomidine, in addition to attenuating sympathoadrenal response to pneumoperitoneum, lesser dose of anesthetics and analgesics can be used, that too without fear of awareness under anaesthesia, thus resulting in an earlier emergence in laparoscopic surgeries. But limitations being, it was an observational case series without any control, also they also used initial loading dose of 1 mcg/kg of dexmedetomidine followed by continuous infusion of 0.2 mcg/kg/hour that led to statistically significant episodes of bradycardia.

In our study, we strived to find out the minimum required dose of dexmedetomidine infusion, (aim) that can effectively attenuate the hemodynamic response to pneumoperitoneum (primary objective) and is associated with least side effects. At the same time, we aimed to find out if at that dose, it is efficient enough as a synergistic agent to significantly decrease the requirement of anesthetics and analgesics, without affecting depth of anesthesia (secondary objective). By 'minimum required dose' we mean to achieve maximum benefits with minimum side effects in the form of bradycardia, hypotension and excessive sedation.

So, our study was designed with the hypothesis that dexmedetomidine can attenuate the hemodynamic stress response to pneumoperitoneum as well as has significant synergistic effect, that too at only infusion dose of 0.5 mcg/kg/hour, without any initial bolus, thus avoiding any unwanted side -effects.

Pilot study done on 40 patients guided us in selection of 0.5 mcg/kg/hour as the optimal dose. While 0.4 mcg/kg/hour was found to be sufficient in ASA I patients, but not in ASA II patients, thereby choosing the above dose.

MATERIALS AND METHODS

After institutional ethical committee permission. (reference no. IEC - 11320; dated 19-06-2023), a prospective randomized double blind control trial was designed in 60 ASA 1 and 2 patients undergoing elective laparoscopic surgery under GA, duration 1-2 hours after informed written consent. The clinical trial was registered at Clinical Trials Registry India dated 25-07-2023 with Trial Registration no.: CTRI/2023/07/055718. All the procedures were conducted in accordance with the principles of the 2013 Declaration of Helsinki.

The sample size was calculated using the formula:
$N = 2\,[(Z_1\text{-}\alpha/2 + Z_1\text{-}\beta) / d]^2 \times s^2$

Where $Z_1\text{-}\alpha/2 = 1.96$ (for 95% confidence), $Z_1\text{-}\beta = 0.84$ (for 80% power), d = 4 (difference between treatment effects) [MAP (at 5 minutes) from Jan S *et al*., [26], study], and s = 9 (pooled standard deviation). This gave a sample size of 27 per group. After adjusting for 10% attrition, the final sample size was 30 per group.

All the 60 patients were double-blinded and randomly assigned into either of the two groups based on the computer-generated random allocation list by an anaesthesiologist not involved in the study and data collection. The study group I(dexmedetomidine) received dexmedetomidine 0.5 mcg/kg/hr prepared by adding 200 mcg (2 ml) of dexmedetomidine in 38 ml of 0.9% NS in concentration of 5mcg/ml. The control group II(normal saline [NS]) received 0.9% NS @ 0.5 mcg/kg/hr. The preparation of the study drug was performed by an anaesthesiology assistant who was not part of the study protocol and it was administered using a syringe pump by an anaesthetist who was not aware of the study protocol. Decoding of blinding to the anaesthetist involved in the study was done only at the time of data analysis.

GROUPS

Group I (n =30)

Dexmedetomidine group- Study drug infusion was started @ 0.5 mcg/kg/hour, without any initial bolus, after securing an iv line before giving any premedication, and continued till deflation of pneumoperitoneum.

Group II (n = 30): Control group-0.9% saline was given at same rate and duration.

Exclusion Criteria

Patient not giving the consent, ASA grade III and IV; patients allergic to dexmedetomidine, coexisting cardio-respiratory disease e.g. ventricular dysfunction, AV Block, chronic use of beta blocker or opioids, liver or renal disease, morbid obesity i.e., BMI≥30 Kg/m^2 , pregnancy and lactation.

Flow chart of the study design is presented in figure1.

After pre-anesthetic checkup, and standard pre-op order protocol, written, informed consent in their language was taken from patients. The patient was taken into the O.T. on the day of surgery and all standard monitors were attached including five lead continuous Electrocardiogram (ECG) for HR and Rhythm monitoring, blood pressure cuff (NIBP), oxygen saturation probe for SpO2 and entropy. A peripheral iv line was secured, crystalloid infusion along with drug infusion were started in all the patients after computer generated random allocation of the 2 groups as mentioned above. In each patient, we ensured adequate intravascular fluid status throughout intraoperative period based upon fasting duration, IVC-CI and intraoperative haemodynamics.

After start of the allocated drug infusion, patients were given i.v. pre- medication using midazolam 0.02mg/kg, glycopyrrolate 10mcg/kg and injection ondansetron 0.1mg/kg. For analgesia, fentanyl 2 mcg/kg was given iv. After pre- oxygenation for three minutes, patients were induced with propofol 1-2mg/kg IV; dose titrated to achieve entropy of 40-60 and that dose was considered as the induction dose in each patient. Endotracheal intubation was facilitated with atracurium 0.5mg/kg i.v., local anaesthetic 0.25 %bupivacaine was infiltrated at the site of port insertion. Anaesthesia was maintained with oxygen: nitrous-oxide (40:60) and isoflurane 0.2 -1.0 volume%, with the target to maintain entropy between 40-60, to ensure adequate depth of anaesthesia. The CO_2 gas was insufflated at the rate 3–5 L/min maintaining the IAP of 10–12 mmHg. The operating table was placed in reverse trendelenburg position (30° head up) and 20° left tilt during the surgery in all the patients. ETCO2 was maintained between 30 to 35 mm Hg.

HR and BP response to pneumoperitoneum were monitored. Intraoperative anesthetic requirement was guided by entropy and haemodynamics (HR and BP, end point for requirement for both was considered a 20% increase from baseline value). The anaesthesiologist was permitted to treat any haemodynamic variation in the form of HR and BP of more than 20% of baseline despite supplementing analgesia by injection fentanyl 0.5mcg/kg and increasing isoflurane to 1.2%, with incremental doses of esmolol and NTG, provided both SE and RE were around 40-60. Injection Paracetamol at 15mg/kg and diclofenac sodium aqueous 75mg were given IV in both the groups as a part of multi-modal analgesia.

Hypotension i.e. NIBP< 20% of the baseline or SBP <90mm hg were treated by bolus of intravenous crystalloid and Bradycardia, defined HR<50/ min was managed with 0.01- 0.02mg/kg atropine. Study drug infusion in both the groups was stopped at the time of end of pneumoperitoneum. Isoflurane was also discontinued at end of pneumoperitoneum. Nitrous oxide was discontinued after skin closure in both the patients. Residual neuromuscular blockade was reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.01 mg/kg IV slowly.

Tracheal extubation was done when respiration was regular with good tidal volume and adequate muscle tone was achieved. Baseline HR, BP and entropy were recorded before induction, during anaesthesia induction, intubation and then at every 5 minutes interval till 10 minutes after extubation (primary outcome measures). Depth of anaesthesia was monitored by entropy analysis at 5 minutes interval. MAC of isoflurane and total intraoperative analgesic consumption in form of opioids was noted in all the patients (secondary outcome measure).

Emergence time was noted in both the groups measured from time of incision closure till extubation (secondary outcome measure). Immediately after extubation sedation was assessed with Modified Ramsay sedation score and recovery was assessed by Modified Aldrete score.

Side effects in the form of significant hypotension, bradycardia, excessive sedation, respiratory depression, if any were noted (secondary outcome measure).

Statistical Analysis: The results obtained in the study are presented in tabulated manner. The final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0.

Quantitative variables were analyzed using independent t -test and qualitative variables by Chi-Square test. P value of less than 0.05 was considered statistically significant.

OBSERVATION AND RESULTS

Age, weight, height, gender ratio, ASA physical status, duration of surgery and duration of pneumoperitoneum were comparable between both the groups [Table 1]. There was no significant difference in the baseline mean systolic blood pressure, diastolic blood pressure, and heart rate in patients of two groups. [Table 2]

HR was significantly low in study group (Group

I) than the control group (Group II) at 5 minutes, at 10 minutes, at 15 minutes, at 20 minutes, (i.e. during the period of pneumoperitoneum); at 25 minutes, at 30 minutes, (at the time of extubation) at 35 minutes, at 40 minutes (in the recovery period) (p value<0.05). [Table 3]

Systolic blood pressure was significantly low (mmHg) in the study group than the control group during the period of pneumoperitoneum (at 5 minutes, at 10 minutes, at 15 minutes, at 20 minutes, at 25 minutes), during extubation (at 30 minutes), and post-extubation (at 35 minutes and 40 minutes) (p value <0.05). [Table 4]

Significant difference was also seen in diastolic blood pressure (mmHg) at 10 minutes, at 15 minutes, at 20 minutes, at 25 minutes, at 30 minutes between group I and II. (p value <0.05) [Table 5]

As far as synergistic effects of dexmedetomidine are concerned, we observed significant reduction in the MAC-ratio of end tidal isoflurane at 5 minutes, at 10 minutes, at 15 minutes, at 20 minutes, at 25 minutes in group I compared to group II. (p value <0.05) as shown in table 6 and figure 2. The peak difference in MAC was seen beginning at 10 minutes from the start of infusion and continued throughout the period of pneumoperitoneum in the dexmedetomidine group. [Table 6, Figure 2]

The mean dose of induction agent, Propofol was significantly more in group II(142.33 ± 15.47 mg), than that in group I, where it was 112.67 ± 13.88 mg (p value < .0001). [Table 7]

The intra-operative requirement of fentanyl was significantly higher in group II (142.67 ± 20.46) as compared in group I (122.67 ± 20.33mg)(p value <0.001). [Table 7]

As far as haemodynamic side effects are concerned, no statistically significant difference was found for bradycardia or hypotension between the groups (p = 1.0 for both) .[Table 8]

As shown in figure 5 and table 9 the mean emergence time in group I was significantly less compared to group II (2.06 ± 0.58 minutes vs 3.46 ± 0.89) (p value <.0001).

The mean modified Ramsay sedation score in group I was significantly lower than in group II (1.9 ± 0.48 vs 2.97 ± 0.49) (p value<0.0001).

The mean modified Aldrete's score in group I was 8.23 ± 0.43, which was significantly higher than in group II, where it was 7.53 ± 0.51 (p value <0.0001). The entropy was maintained between 40-60 in both the groups as a marker for adequate depth of anaesthesia [Figure 3, Figure 4].

Table 1: Patient characteristics and duration of surgery and pneumoperitoneum

	Group 1 (Dexmedetomidine group) Mean ±SD	**Group 2 (Normal saline) Mean ±SD**	**P value**	**Statistical Significance**
Age (years)	45.23±11.84	44.97 ± 9.38	0.923	Non significant
Gender (F/M)	22/8	20/10	0.573	Non significant
BMI (kg/m2)	22.77 ± 2.41	23.02 ± 2.03	0.657‡	Non significant
ASA (1/2)	23/7	16/14	0.058†	Non significant
Surgery time (minutes)	27.6 ± 7.98	25.13 ± 4.22	0.142‡	Non significant
Pneumoperiton Eum time (minutes)	21.27 ± 8.17	18.33 ± 4.25	0.088‡	Non significant

Values are presented as Mean ± SD or number.
Group 1: Dexmedetomidine group; Group 2: Normal saline group.
BMI: body mass index; SD: standard deviation; M: male; F: female; ASA: American Society of Anesthesiologists physical status.
†p value calculated using Chi-square test (for categorical variables).
‡p value calculated using Student's t-test (for continuous variables).

Table 2: Pre operative vitals in Group 1 and Group 2

	Group 1		**Group 2**			
Parameters	**Mean**	**SD**	**Mean**	**SD**	**P value**	**Statistical significance**
HR	86.33	18.03	82.2	12.05	0.301	NS
SBP	137.2	20.29	133.77	17.35	0.484	NS
DBP	83.7	10.18	84.73	10.17	0.696	NS

Values are presented as Mean ± SD.
Group 1: Dexmedetomidine group; Group 2: Normal saline group.
HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; SD: standard deviation; NS: not significant.
P values calculated using Student's t-test.

Table 3: Comparison of heart rate (per minute) between group I and II.

Heart rate (per minute)	**Group I (Dexmedetomidine)** Mean ± SD	**Group II (Norma l saline)** Mean ± SD	**P value**	**Statistical significance**
At baseline	86.33 ± 18.03	82.2 ± 12.05	0.301	NS
At 0 mins	86.33 ± 18.03	82.2 ± 12.05	0.301	NS
At 5 mins	74.13 ± 9.83	96.5 ± 9.53	<.0001	S
At 10 mins	73.77 ± 11.49	101.9 ± 8.21	<.0001	S
At 15 mins	76.47 ± 8.46	92.37 ± 6.72	<.0001	S
At 20 mins	77.7 ± 9.07	90.4 ± 6.41	<.0001	S
At 25 mins	77.43 ± 8.14	91 ± 9.08	<.0001	S
At 30 mins	81.08 ± 8.52	95.84 ± 8.03	<.0001	S
At 35 mins	79.88 ± 8.86	90.45 ± 11	0.011	S
At 40 mins	79.82 ± 5.78	99 ± 7	0.0004	S

Values are presented as Mean ± SD.
Group I: Dexmedetomidine group; Group II: Normal saline group.
SD: standard deviation; NS: not significant; S: significant.
P values calculated using Student's t-test.

Table 4: Comparison of systolic blood pressure (mmHg) between group I and II

	Group I	**Group II**	**P value**	
Systolic pressure (mm H g)	**(Dexmedetomidin e) Mean ± SD**	**(Normal saline) Mean ± SD**		**Statistical significance**
At baseline	137.2 ± 20.29	133.77 ± 17.35	0.484	NS
At 0 mins	137.2 ± 20.29	133.77 ± 17.35	0.484	NS
At 5 mins	121.4 ± 17.56	133.73 ± 23.82	0.026	S
At 10 mins	114.5 ± 12.3	142.27 ± 24.96	<.0001	S
At 15 mins	120.17 ± 9.78	135.63 ± 15.19	<.0001	S
At 20 mins	122.8 ± 9.3	133.37 ± 13.07	0.0006	S
At 25 mins	122.29 ± 11.74	133.2 ± 19.44	0.012	S
At 30 mins	122.75 ± 10.84	134.62 ± 19.15	0.012	S
At 35 mins	123 ± 11.05	137.18 ± 17.34	0.015	S
At 40 mins	126.18 ± 10.05	134.67 ± 13.01	0.243	S

Values are presented as Mean ± SD.
Group I: Dexmedetomidine group; Group II: Normal saline group.
SD: standard deviation; NS: not significant; S: significant.
P values calculated using Student's t-test.
mmHg: millimeters of mercury.

Table 5: Comparison of diastolic blood pressure (mmHg) between group I and II

Diastolic blood pressure(m mHg)	**Group I (Dexmedetomidi ne)** Mean ± SD	**Group II (Normal saline)** Mean ± SD	**P value**	**Statistical significance**
At baseline	83.7 ± 10.18	84.73 ± 10.17	0.696	NS
At 0 mins	83.7 ± 10.18	84.73 ± 10.17	0.696	NS
At 5 mins	76.6 ± 11.15	83.97 ± 13.37	0.024	NS
At 10 mins	72.73 ± 7.7	86.77 ± 13.39	<.0001	S
At 15 mins	76.8 ± 7.76	84.3 ± 9.06	0.001	S
At 20 mins	78.73 ± 6.9	86.1 ± 8.03	0.0003	S
At 25 mins	77.14 ± 8.18	82.93 ± 10.47	0.023	S
At 30 mins	78.79 ± 7.44	84.04 ± 9.73	0.041	S
At 35 mins	78.56 ± 6.04	83.18 ± 11.89	0.255	NS
At 40 mins	80.73 ± 8.73	89.33 ± 11.02	0.174	NS

Values are presented as Mean ± SD.
Group I: Dexmedetomidine group; Group II: Normal saline group.
SD: standard deviation; NS: not significant; S: significant.
P values calculated using Student's t-test.
mmHg: millimeters of mercury

Table 6: Comparison of MAC-ratio between group I and II

MAC-Ratio	Group I (Dexmedetomidi ne) Mean ± SD	Group II (Normal saline) Mean ± SD	P value	Statistical significance
At baseline	0 ± 0	0 ± 0	1	NS
At 0 mins	0 ± 0	0 ± 0	1	NS
At 5 mins	0.53 ± 0.17	0.71 ± 0.19	0.0002	S
At 10 mins	0.63 ± 0.1	0.98 ± 0.09	<.0001	S
At 15 mins	0.62 ± 0.09	1.04 ± 0.11	<.0001	S
At 20 mins	0.55 ± 0.15	0.97 ± 0.16	<.0001	S
At 25mins	0.49 ± 0.23	0.74 ± 0.31	0.001	S
At 30 mins	0.4 ± 0.26	0.4 ± 0.31	0.962	NS
At 35 mins	0.32 ± 0.26	0.31 ± 0.26	0.877	NS
At 40 mins	0.23 ± 0.25	0.2 ± 0	0.72	NS

Values are presented as Mean ± SD.
Group I: Dexmedetomidine group; Group II: Normal saline group.
MAC: minimum alveolar concentration; SD: standard deviation; NS: not significant; S: significant.
P values calculated using Student's t-test.

Table 7: Comparison of dose of Propofol and Fentanyl between group I and II

Group	Dose of propofol (Mean ± SD)	Dose of fentanyl (Mean ± SD)
Group I (Dexmedetomidine)	112.67 ± 13.88	122.67 ± 20.33
Group II (Normal Saline)	142.33 ± 15.47	142.67 ± 20.46
P value	<0.0001	<0.0001

Values are presented as mean ± SD.
Group I: Dexmedetomidine group; Group II: Normal saline group.
SD: standard deviation.
P values calculated using Student's t-test

Table 8: Comparison of side-effects: bradycardia and hypotension

Side effects	Bradycardia	Hypotension
Group I (Dexmedetomidine)	1	0
Group II (Normal Saline)	0	0
P value	1.0	1.0

Values are presented as number of patients.
Group I: Dexmedetomidine group; Group II: Normal saline group.
P values calculated using Fisher's exact test.
Bradycardia: heart rate <60 beats per minute; Hypotension: systolic blood pressure <90 mmHg.

Table 9: Comparison of Emergence time, Sedation score and Recovery score between Groups I and II

Parameter	Group 1	Group 2	P value	Statistical significance
	Mean ± SD	Mean ± SD		
Emergence Time	2.06 ± 0.58	3.46 ± 0.89	<.0001	S
Modified Ramsay sedation score	1.9 ± 0.48	2.97 ± 0.49	<.0001	S
Modified Aldrete's score	8.23 ± 0.43	7.53 ± 0.51	<.0001	S

Values are presented as mean ± SD.
Group 1: Dexmedetomidine group; Group 2: Normal saline group.
SD: standard deviation; S: significant.
Emergence time: measured from time of incision closure till extubation
Modified Ramsay sedation score: assesses sedation level (higher score = more sedation).
Modified Aldrete's score: assesses recovery after anesthesia (higher score = better recovery).
P values calculated using Student's t-test.

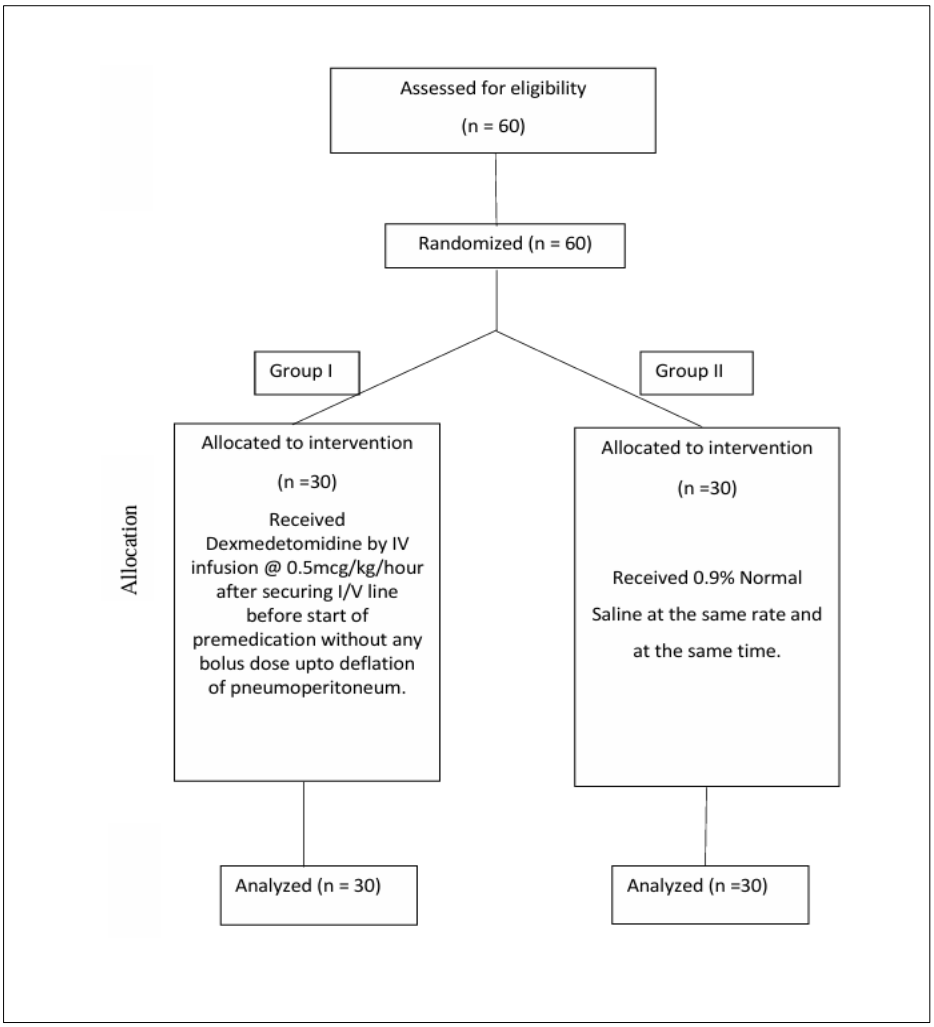

Figure 1: Consort flow diagram

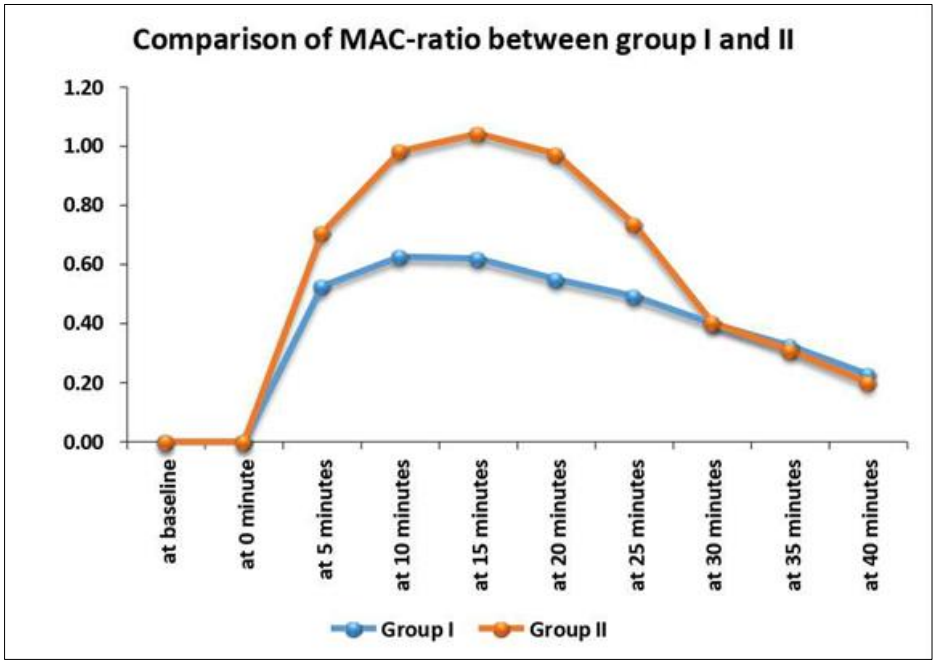

Figure 2: Comparison of trend of MAC- ratio at different time intervals between group I and group II

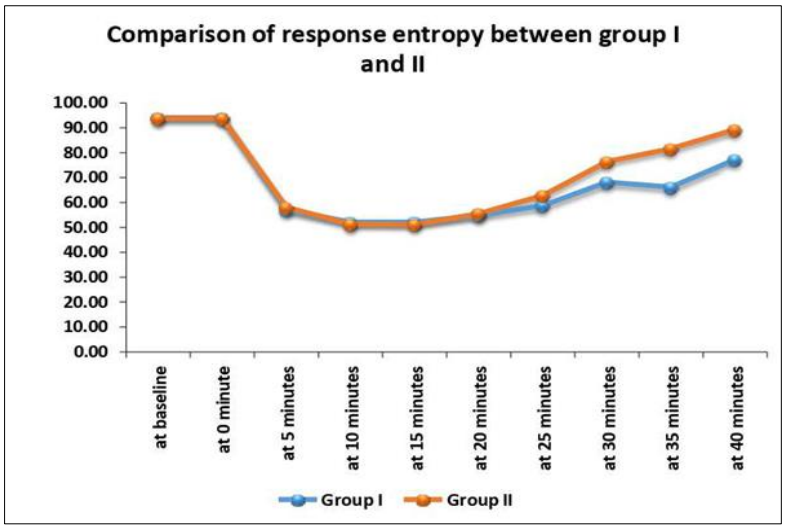

Figure 3: Comparison of trend of response entropy at different time intervals between group I and group II

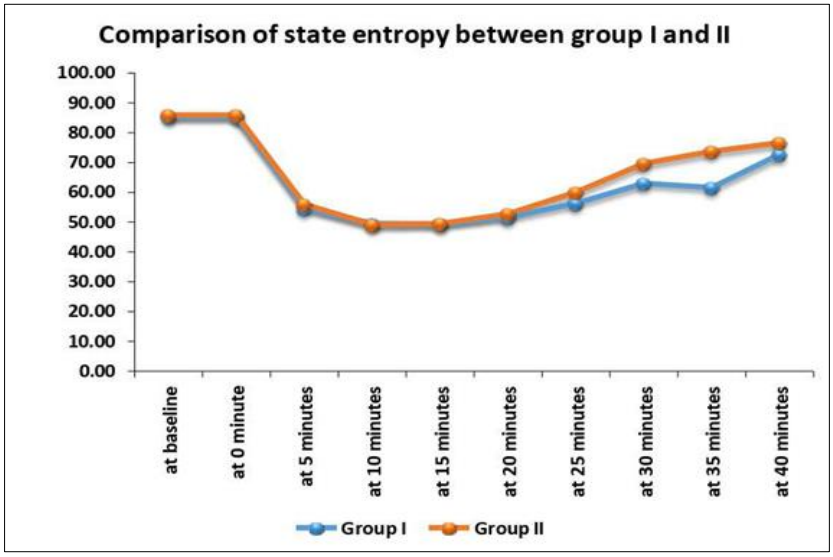

Figure 4: Comparison of trend of state entropy at different time intervals between group I and group II

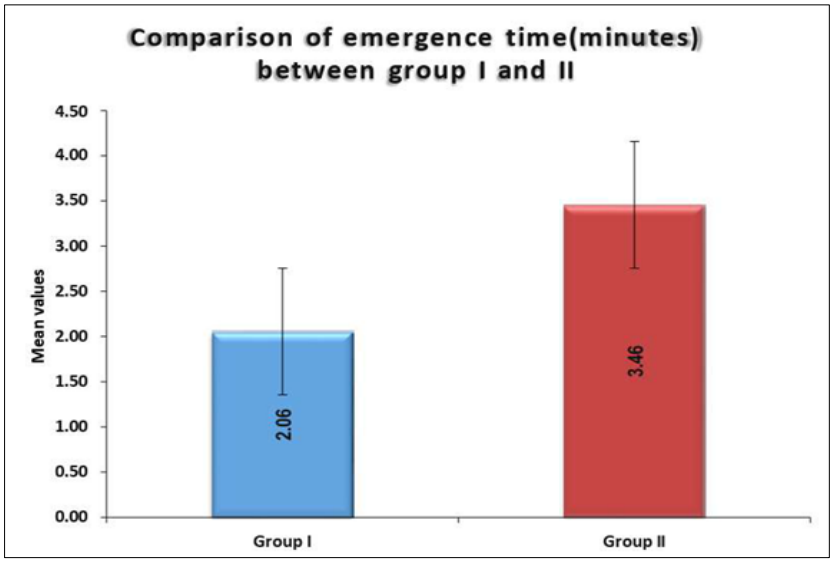

Figure 5: Comparison of emergence time (minutes) between group I and group II

DISCUSSION

Many previous studies have highlighted the hemodynamic changes during pneumoperitoneum in laparoscopic surgeries [1-9]. In our study also, we observed rise in systolic blood pressure, diastolic blood pressure and heart rate during the entire pneumoperitoneum period in the control group (group II) due to raised IAP as observed by the previous studies [1-9], including landmark study by Loris *et al*., [9], Prolonged intraoperative increase of 20 mm of Hg or more in MAP and tachycardia are poorly tolerated by patients with pre-existing cardiac disease [18]. So, a drug that can efficiently attenuate these haemodynamic responses in laparoscopic surgeries, may be of immense use in decreasing the morbidity especially in high-risk cardiac patients.

Dexmedetomidine, a selective central α2-adrenergic agonist is eight times more specific for α2 receptors than clonidine [12-16], making it more effective than clonidine. It has sedative, anxiolytic, analgesic, and sympatholytic properties. It produces these effects by inhibiting central sympathetic outflow by blocking the alpha receptors in the brainstem, thereby inhibiting the release of norepinephrine which is beneficial to keep hemodynamic stability during intraoperative stress [18, 19].

We too found in our study that contrary to control group, both systolic and diastolic blood pressures, as well as heart rate, remained within 20% of baseline throughout the pneumoperitoneum period in the dexmedetomidine group, with statistical significance ($p < 0.05$). None of the patients in dexmedetomidine group required either esmolol or nitroglycerine to counter the tachycardia and hypertensive effects of pneumoperitoneum.

Similar findings have been seen in previous studies by Masoori *et al*., [17], Vora *et al*., [16], Rajmohan *et al*., [20], and Ghodaki P.S. *et al*., [13], but all of these studies used loading dose of 1mcg/kg or 0.5mcg/kg/hour [18], followed by different maintenance doses of 0.2mcg/kg/h [13-20], 0.3 mcg/kg/hour and 0.6mcg/kg/hour [17], and 0.5 mcg/kg [16]. They also noted statistically significant episodes of bradycardia at these dosages [13-17].

Our study differs in the fact that with the timely start of dexmedetomidine infusion, 10-15 minutes before the onset of pneumoperitoneum, we observed effective sympatholytic effect of dexmedetomidine at the infusion dose of 0.5 mcg/kg/hour without any statistically significant episode of bradycardia, hypertension or hypotension and excessive sedation, most probably because we avoided the initial bolus dose of dexmedetomidine.

The possible reason for effectiveness of infusion dose, without any initial loading dose, in attenuating the sympathoadrenal response to pneumoperitoneum, as is found in our study is that with ongoing therapy with a slow infusion, fall in blood pressure and control of HR is observed within 10-15 minutes, mediated by central α_2A-AR, that decreases the release of noradrenaline from the sympathetic nervous system [21]. With the timely start of dexmedetomidine infusion after securing iv line, it had enough time to control hemodynamic changes that happen with the onset of pneumoperitoneum. Rapid infusion with a loading dose, in contrast may cause a transient increase in blood pressure and a reflexive drop in HR by acting on peripheral α_2B-AR vasoconstriction and the activation of peripheral α_1 post-junctional adrenergic receptors [22], leading only to undesirable effects.

Moreover, various doses ranging from 0.2mcg/kg/hour to 0.8 mcg/kg/hour following 0.5mcg/kg or 1 mcg /kg bolus have been studied by various authors primarily with the only goal of attenuating the hemodynamic changes during pneumoperitoneum [15-23].

But it is a known fact that dexmedetomidine, by acting on central α2 receptors at the brainstem, locus coeruleus and in dorsal horn neurons of the spinal cord also potentiates the effects of all intraoperative anesthetics [13], leading to intraoperative MAC-sparing and opioid sparing effects, thus facilitating smooth and early emergence from anesthesia, without any respiratory depression. All these effects make dexmedetomidine an overall more valuable anesthetic adjuvant [11-29].

Our study uniquely establishes that even without an initial bolus, a continuous infusion at 0.5 mcg/kg/hour when started well in time before the onset of pneumoperitoneum not only effectively attenuates the hemodynamic stress response, but in addition provides other benefits due to its synergistic effect.

As far as the efficacy of other benefits of dexmedetomidine are concerned, we observed a 20.8% decrease in the induction dose of propofol (112.67 mg± 13.88) in group I, compared to control (142.33mg ± 15.47) reinforcing the anaesthetic-sparing role of dexmedetomidine due to its synergistic effect. This observation is consistent with findings by Le Guen *et al*., [25], where patients who were given dexmedetomidine 1mcg/kg over 10 minutes followed by maintenance of 0.5mcg/kg/hour throughout the surgery, had 29% decrease in the propofol requirement than the placebo group. In another study by Vishwanath *et al*., [26], propofol requirements were 26.6% lesser in group where premedication with 1mcg/kg of dexmedetomidine was given ($P < 0.001$). Also, in study by Ghodki PS [13]. 62.5% reduction was observed in dexmedetomidine group when they titrated the dose to achieve entropy of 40-60. This much reduction was found when they used initial loading dose of dexmedetomidine @ 1 mcg/kg for

15 minutes before pre-medication, contrary to our study where we did not use an initial bolus and still found 20.8% reduction in propofol induction dose.

Dexmedetomidine also exhibited a significant MAC-sparing effect on volatile anaesthetic agents by inhibiting the central noradrenergic transmission. Usually, for maintenance of anesthesia, end- tidal isoflurane concentration required is 1.0 to 1.2%. It was observed in our study group, that the same was between 0.4 to 0.6% (more than 50% reduction seen with only infusion dose of dexmedetomidine) throughout surgery achieving adequate depth of anesthesia (entropy 40-60); with peak requirement at the beginning of surgery. Aanta R *et al*., [27], in 1997 published the first report showing a reduction of maintenance concentration of inhalation agent with the use of dexmedetomidine. Findings similar to our study have been found in study by Vora *et al*., [16], but they did not measure depth of anesthesia. In an observational study by Poonam S. Ghodaki P S *et al*., [13], the end-tidal concentration of isoflurane was 35 to 50 % less than routine concentration of 1.5 to 1.8% isoflurane similar to findings by Khan ZP *et al*., [28], where they used dexmedetomidine at bolus dose of 1mcg/kg followed by 0.2mcg/kg/hour maintenance infusion [13], vs 1mcg/kg followed by 0.5mcg/kg/hour [28], respectively ($p<0.05$). Our findings also align with the results of Aho *et al*., [19], a study in patients who underwent open abdominal hysterectomy, as far as effect of dexmedetomidine on reduction in requirement of isoflurane is concerned.

Importantly, even with so much reduction in the requirement of inhalational agents and entropy between 40-60, none of the patients in our study group required any beta-blockers or vasodilator intraoperatively. Whereas in around 30% of patients in control group there was a need to use vasodilator or beta- blockers even after using higher concentration of isoflurane 1.2%, to achieve haemodynamic stability.

Studies have found opioid – sparing effect of dexmedetomidine in the peri-operative period.[13,25] Its central α2 receptor activation at locus coeruleus suppresses norepinephrine release and this reduces the propagation of pain signals and leads to analgesia. In dorsal horn neurons of spinal cord, it reduces the release of pain-transmitting neurotransmitters like substance P and glutamate and hyperpolarizes spinal interneurons, directly inhibiting pain transmission [13-25].

Fentanyl requirement in our study was 2.0 mcg /kg in the dexmedetomidine group whereas additional fentanyl top up of 0.5 mcg /kg was required in one- third of patients in the control group. Similar findings have been observed in study by Ghodki PS *et al*., [13].

Using a drug with mechanism of action that seems to decrease the requirement of anesthetics and analgesics may lead to apprehension regarding inadequate anaesthesia. So, we monitored the depth of anesthesia (DOA) using entropy in our study to ensure adequate DOA - a limitation in several earlier studies [16-19].

Entropy has two indices; State Entropy (SE) and Response Entropy (RE), calculated from electroencephalogram (EEG) data to monitor the depth of anesthesia in patients. State Entropy reflects the EEG-dominated part, primarily the brain activity and hence depth of hypnosis. Response Entropy uses a broader frequency range, to include frontal electromyographic activity, which can indicate patient responses to external stimuli like pain or movement [24]. Aim is to keep both entropy values between 40-60 to ensure adequate DOA as well as nociception [13]. We found that in dexmedetomidine group, target entropy values were maintained even with significantly less requirement of i.v. and inhalational anesthetics and opioids, ensuring that patient is pain free as well as in adequate plane of anesthesia.

Contrary to some reports citing delayed recovery with dexmedetomidine, our study observed earlier emergence and significantly lower sedation scores in the intervention group, likely due to the avoidance of a bolus dose of dexmedetomidine and reduced overall anaesthetic exposure leading to a more balanced anaesthesia care. Patients were significantly less sedated in dexmedetomidine group compared to controls with Mean Ramsay Sedation Scores (1.9 ± 0.48 vs 2.97 ± 0.49, $p < 0.0001$). Patients were able to respond to commands when stimulated. Similar findings of earlier emergence from anesthesia without undue sedation were seen using dexmedetomidine in laparoscopic surgeries by Ghodaki PS *et al*., [13], and Vora *et al*., [16].

As far as haemodynamic side effects are concerned, only one episode of transient bradycardia was observed in the dexmedetomidine group, that too at the time of commencement of pneumoperitoneum, may be that was due to peritoneal stretching leading to vagus stimulation, promptly managed with atropine, further strengthening the safety of the studied dose. Study by Rani HB *et al*., [18], has also mentioned lowest incidence of bradycardia at 0.5 mcg/kg/hour. Whereas studies that have used bolus or higher concentration of dexmedetomidine have seen episodes of bradycardia as side effect [13-17].

Limitations

The study was limited to ASA I and II patients; further research is warranted to assess efficacy and safety in higher-risk populations and elderly population.

To conclude, Dexmedetomidine infusion without any initial bolus when started in time efficiently suppresses haemodynamic stress response to pneumoperitoneum, and also has significant synergistic effect, as it leads to lower overall anaesthetic

requirements, without affecting depth of anesthesia as ensured with entropy, with added advantage of early and smooth emergence in ASA I-II patients undergoing laparoscopic surgery. And these effects are best seen at a dose of 0.5 mcg/kg/hour along with lowest reported side effects, making it an ideal anesthetic adjuvant in laparoscopic surgeries.

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