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STUDY OF EFFECTS OF INTRAVENOUS INFUSION OF DEXMEDETOMIDINE ON PERI-OPERATIVE HAEMODYNAMIC CHANGES AND POST-OPERATIVE RECOVERY IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT
Background: In present era, laparoscopic cholecystectomy is the preferred surgery for gall stones. Along with its benefits, it is associated with a significant sympathoadrenal stress response. Various drugs have been used to allay the same. Dexmedetomidine a selective α-2 agonist with sedative, analgesic and sympatholytic properties. The present study was therefore undertaken to evaluate the efficacy of intraoperative administration of 0.4 mcg/kg/hr of Dexmedetomidine infusion in patients undergoing laparoscopic surgeries. The primary objective was to study the impact of Dexmedetomidine in reducing the hemodynamic stress response to laryngoscopy, intubation, pneumoperitoneum, and extubation and secondary objective was to assess the post-operative sedation levels, extubation time and analgesic requirements and adverse effects if any.
MATERIALS AND METHODS: The present study was a prospective, randomized, double blinded carried out on 100 patients of ASA 1 in the age group of 18-65 years which were randomly divided into two groups of 50 each: Group D; patients received inj. Dexmedetomidine infusion at a rate of 0.4 mcg/kg/hr from 15 minutes prior to induction to the completion of operation while Group C; patients received normal saline infusion at the same rate as a placebo.
RESULTS: Both the groups were comparable with respect to the age, gender and weight. Following laryngoscopy, tracheal intubation, pneumoperitoneum formation, and extubation, there was a significant hemodynamic stress response in Group C. When comparing the Group D to the Group C, the hemodynamic stability was considerably more in Group D. ($p<0.05$). Time for extubation and eye-opening was not prolonged in Group D. ($p<0.001$). In terms of visual analogue score, the patients in Group D had less analgesic demands for the first 24 hrs following surgery. There were no noticeable adverse effects.
CONCLUSION: A low dose infusion of Dexmedetomidine administered @ 0.4 mcg/kg/hr without prior bolus can be used as an anaesthetic adjuvant in attenuating hemodynamic response to laryngoscopy, intubation, pneumoperitoneum and extubation. It contributes to a lighter sedation without affecting extubation time, as well as a reduction in the postoperative analgesic requirements and is not associated with any major adverse effects.

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INTRODUCTION

Laparoscopic cholecystectomy has become the gold standard for gall bladder disease. It offers significant benefits such as a small incision with reduced postoperative pain, faster recovery, less postoperative ileus and improved postoperative pulmonary function compared to traditional open surgeries. Despite its multiple benefits, any laparoscopic surgery has many challenges for its successful anaesthetic management.[1]

The pressor response (stress response) increases sympathetic and sympathoadrenal activity due to laryngoscopy and intubation. Creation of pneumoperitoneum results in an increase in the plasma level of norepinephrine, epinephrine and plasma renin activity. These changes together lead to increase in arterial pressure, pulmonary and systemic vascular resistance and decrease in cardiac output.[2] Carbon dioxide (CO_2) absorption is also affected by an increase in intra-abdominal pressure (IAP) leading to increased blood pressure, arrhythmias, increased myocardial contractility, and sensitization of the myocardium to catecholamines. These effects are exaggerated beyond 15 mm Hg of IAP. Trendelenburg position is associated with an increase in venous return and pulmonary capillary wedge pressure, which prevents a decline in cardiac output after insufflation. In contrast, the reverse Trendelenburg position causes diminished venous return, leading to decreased cardiac output.[3]

Blunting of pressor response can be achieved by various methods like the use of low IAP, abdominal lift methods but these all have practical implications. A wide array of drugs in use are benzodiazepines, opioids, vasodilators, propofol infusion, β-2 blockers and α-2 agonists to attenuate sympathoadrenal stimulation.[4]

Dexmedetomidine is a potent α-2 adrenergic agonist with eight times greater affinity for α-2 adrenergic receptors but has less affinity for α-1 receptors as compared to clonidine. Dexmedetomidine has sedative, hypnotic, sympatholytic, anxiolytic and analgesic properties without causing much side effects. The sympatholytic effect of Dexmedetomidine decreases mean arterial pressure (MAP) and heart rate (HR) by reducing norepinephrine release. There is around 90% decrease in levels of serum catecholamine which attenuates the stress response.[5] Sedative effect produced by Dexmedetomidine occurs due to decreased activity of the sympathetic nervous system and the level of arousal. As a result, the patient is a calm and can be aroused easily to full consciousness.[6]

METHODS

The study was conducted in the Department of Anaesthesiology over a period of 18 months from 1st April 2020 to 30th September 2021. Study was prospective, randomized, double-blinded and involved one hundred patients of either sex in the age group of 18-65 years, belonging to Class 1 American Society of Anaesthesiologists (ASA). Patients with associated medical ailments like diabetes mellitus, hypertension, cardiac disease,

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hypothyroidism, patients on drugs like β-blockers and calcium channel blockers, pregnant or lactating women, morbidly obese patients and patients with known allergic history to α-2 agonists were excluded from the study. Patients were randomised into two groups of 50 patients each as follows:

Group D (study group) comprised of 50 patients and they received Dexmedetomidine infusion at a rate of 0.4 mcg/kg/hr from 15 minutes before induction to the completion of operation while Group C (control group) consisted of 50 patients who received normal saline infusion at the same rate as a placebo.

All the patients were evaluated at least 24 hrs before anaesthesia and surgery. The patients were informed about the anaesthetic procedure and written informed consent was obtained from each patient.Tablet Pantoprazole 40 mg and Tablet Alprazolam 0.25 mg was prescribed the night before surgery and on the morning of surgery. On the day of surgery, vitals in the form of HR and rhythm, systolic blood pressure (SBP), diastolic blood pressure (DBP) and MAP and SpO_2 were recorded in the pre-operative area. A wide bore cannula was placed, and all the patients were pre-medicated with Inj. Glycopyrrolate 0.2 mg intramuscular 45 minutes before induction of anaesthesia. Dexmedetomidine infusion was started in the Group D patients at 0.4 mcg/kg/hr, while normal saline infusion was started at the same rate in the Group C patients. Inj. Ringer lactate (RL) was administered as maintenance fluid. After 15 minutes of Dexmedetomidine/normal saline infusion, Inj. Fentanyl 1 mcg/kg and Inj. Ondansetron 4 mg intravenous were given.

Pre-oxygenation was done for 3 minutes, followed by induction with Inj. Propofol 2mg/kg and Inj. Vecuronium bromide 0.1mg/kg intravenous. Patient was intubated and anaesthesia was maintained on N_2O:O_2 (50:50) and Isoflurane. Throughout the surgery, IAP's were kept between 10 and 12 mm Hg. The patients were ventilated to maintain an $EtCO_2$ of 35-45 mm Hg. Dexmedetomidine/normal saline infusion and anaesthetic agents were stopped after surgery. The reversal was given at a dose of 0.05 mg/kg Neostigmine and 0.01 mg/kg Glycopyrrolate. Extubation time was counted from the stoppage of anaesthetic agents to the extubation.

Vital parameters were monitored in the intra-operative period at 5 minutes intervals throughout the conduct of surgery. The data was analysed at the following intervals: before to commencing the study/control medication infusion, 15 minutes after starting the infusion, before intubation, after intubation, after the formation of pneumoperitoneum, after the release of pneumoperitoneum, before extubation and after extubation.

All the patients were followed for 24 hrs at 6 hrs interval, and the following parameters were recorded: visual analogue score (VAS) and ramsay sedation score (RSS). Inj. Paracetamol 1 gm infusion was used as rescue analgesia as and when required during the first 24 hrs, and the total number of rescue analgesics used were recorded.

Patients were also observed for any adverse effects in the post-operative period.

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Categorical data was summarized using frequency distribution and proportions. Numerical data was summarized using mean and standard deviation. T-test and ANOVA test were used to find the significance difference of continuous variables. The p value < 0.05 was considered significant.

RESULTS

The two groups under study were comparable to each other with respect to age, sex, and weight. (Table 1).

There was no significant difference among the two groups in reference to baseline HR and MAP. In Group C, after starting the infusion there was no significant change in HR and MAP but these increased significantly above pre-infusion level after intubation, after pneumoperitoneum and extubation. ($p<0.001$). In Group D, after starting the infusion, the HR and MAP decreased significantly below the pre-infusion level.HR and MAP remained below pre-infusion level after extubation. (Tables 2 and 3).

The post-operative sedation scores were observed using Ramsay Sedation Score at 0 minute and thereafter at an interval of 6 hrs. The sedation scores were more in group D compared to group C. None of the patients in group D developed significant sedation levels and patients were oriented, tranquil, and co-operative. ($p<0.001$).No significant difference was found between the two groups after 0 mins of extubation to 24 hrs postoperatively.(Figure 1)

A statistically reduction in VAS pain scores in group D when compared to group C at 0-minute following shifting of patient to post-operative area. ($p<0.001$).

Thereafter, no significant difference in VAS pain scores was observed between the two groups.(Figure 2)

The rescue analgesia requirements were more in group C compared to group D.

Nausea and vomiting were seen in 2 patients in the group D and 2 patients in the group C. Dry mouth was noted in 2 patients in the group D and 3 patients in the group C. (Table 4)

Table 1. Demographic Characteristics.

PARAMETERS	**Groups**			**p value**
	Group D (Mean±SD)		**Group C (Mean±SD)**	
Age (yrs)	41.60±11.51		44.38±12.20	0.224
Gender	Male	17(34%)	16(32%)	0.832
	Female	33(66%)	34(68%)	
Weight (kg)	64.78±9.52		64.46±11.35	0.879

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Table 2. Comparison of mean HR (bpm) between the Group D and Group C at various time intervals during the study.

HR (bpm)	Group D (Mean±SD)	Group C (Mean±SD)	p value
Before start of Infusion	76.20±7.77	74.38±6.81	0.176
15 minutes after Infusion	62.88±7.47	73.96±5.96	<0.001
Just before Intubation	62.14±6.99	72.90±5.57	<0.001
Immediately after intubation	64.58±6.76	84.34±7.17	<0.001
After creation of pneumoperitoneum	64.2±6.47	83.22±5.04	<0.001
After release of Pneumoperitoneum	64.32±6.48	84.62±6.26	<0.001
Before extubation	69.98±6.71	85.62±5.50	<0.001
After extubation	70.90±6.71	84.86±5.50	<0.001

Table 3. Comparison of MAP between the two groups at various time intervals during the study.

MAP (mmHg)	Groups		p value
	Group D (Mean±SD)	Group C (Mean±SD)	
Before start of Infusion	92.72 ±5.17	93.74 ±2.29	0.558
15 minutes after Infusion	85.18±5.25	93.98±2.23	<0.001
Just before Intubation	83.72±6.99	92.46±5.77	<0.001
Immediately after Intubation	84.24±5.40	104.26 ±3.88	<0.001
After creation of pneumoperitoneum	83.82 ±5.36	106.98 ±3.79	<0.001
After release of pneumoperitoneum	83.76 ±5.11	108.14±3.71	<0.001
Before Extubation	89.62±7.40	101.34 ±2.95	<0.001
After Extubation	90.44±7.19	100.90 ±2.68	<0.001

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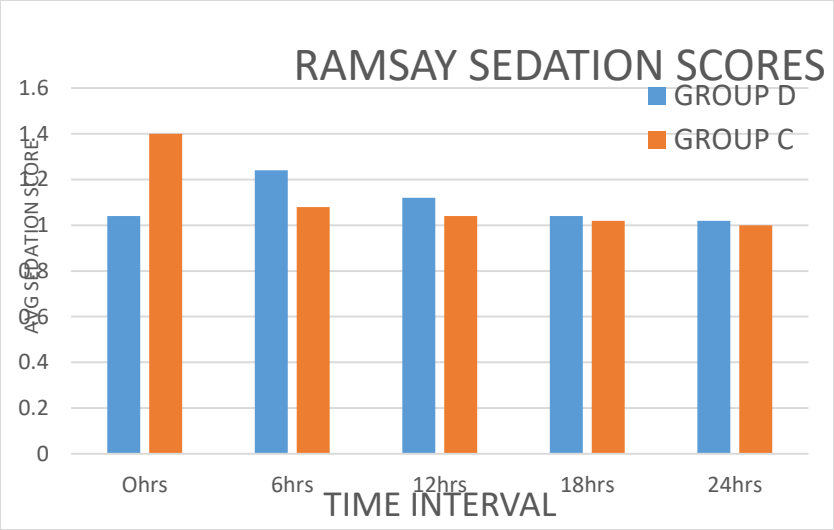

Figure 1: Comparison of sedation scores between the two groups.

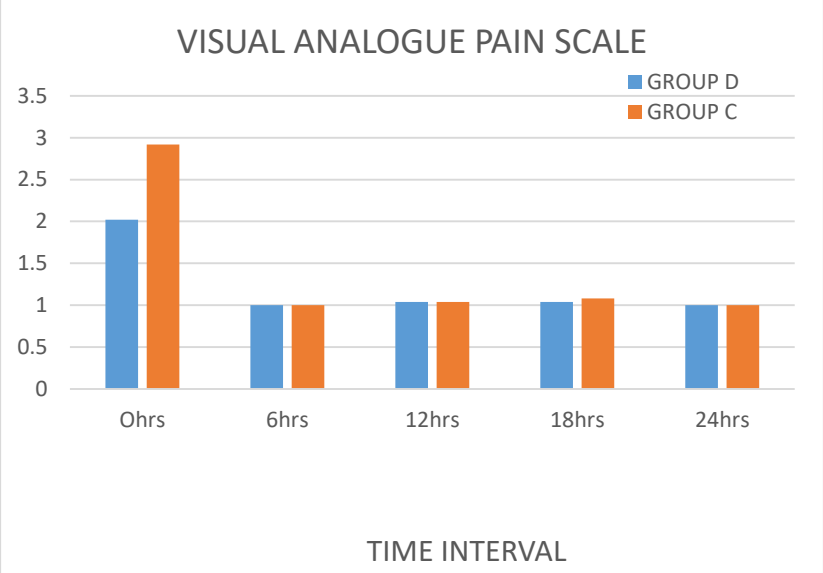

Figure *2*: Comparison of visual analog scores between the two groups.

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Table 4. Comparison of adverse effects between group D and group C.

Adverse effects	Group D	Group C
Respiratory depression	0(0.0%)	0(0.0%)
Nausea and vomiting	2(4.0%)	2(4.0%)
Dry mouth	2(4.0%)	3(6.0%)
Pruritis	0(0.0%)	0.0%

DISCUSSION

Dexmedetomidine acts through three types of α-2 receptors- α-2A, α-2B, and α-2C. The peripheral nervous system contains most of the α-2A adrenoreceptors, whereas the brain and spinal cord contains the α-2B and α-2C adrenoreceptors. Vasoconstriction is caused by postsynaptic α-2 adrenoreceptors in peripheral blood vessels, whereas presynaptic α-2A adrenoreceptors decrease norepinephrine release and reduce vasoconstriction. Stimulation of α-2A and α-2C in locus coeruleus produces sedation. The activation of both α- 2A and α- 2C receptors in the spinal cord reduces pain transmission by lowering substance P release. Dexmedetomidine produces dose-dependent sedation, anxiolysis, analgesia, and blunts the pressor response to anaesthesia and surgery. Dexmedetomidine can be given as a 0.8-1 mcg/kg intravenous bolus over 10-15 minutes, followed by a 0.2-0.7 mcg/kg/hr infusion. When bolus and higher infusion doses of Dexmedetomidine are used, there is an increased incidence of adverse events like hypotension and bradycardia. Omitting bolus dose reduces the side effects and provides better hemodynamic stability as demonstrated by Manne et al.[7]

Therefore in the present study low doses of Dexmedetomidine infusion without a bolus was used to see the effects on hemodynamic changes during intubation, pneumoperitoneum, extubation, analgesic requirement and sedation. Critical incidents such as laryngoscopy and intubation, pneumoperitoneum, and extubation, as demonstrated in group C, dramatically raise the MAP and HR in patients undergoing laparoscopic cholecystectomy. Dexmedetomidine reduces this sympathoadrenal response and improves haemodynamic stability. Reduced HR and systemic vascular resistance are the direct effects of α-2 agonists on the cardiovascular system, resulting in reduction in causing in myocardial contractility, cardiac output and BP. Suppression of norepinephrine release, hypotension and bradycardia arise from stimulation of α-2A receptors in brainstem. When comparing the Dexmedetomidine group to the normal saline group, there was a substantial fall in MAP at various time intervals during the induction phase, pneumoperitoneum extending till the end of the procedure in the Dexmedetomidine group. Our findings are in concordance with Sebastian B et al and Madhuri SR et al who concluded that patients receiving Dexmedetomidine infusion had a significant reduction in MAP throughout the procedure.[6,8]

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Dexmedetomidine offers benefits such as sedation and analgesia in addition to stress response attenuation. Dexmedetomidine's sedative effects are mediated by the α-2A and α-2C adrenoceptor in locus coeruleus. In the present study, patients in group D had a considerably greater sedation scores in the postoperative period than group C. However, none of the patients experienced considerable sedation and they remained cooperative, oriented and calm all the time without requiring any intervention in airway management. Sedation was seen in the initial 30 minutes only in group D($p<0.001$). No significant difference was found between the two groups after 0 mins of extubation to 24 hrs postoperatively.

The activation of both α- 2A and α- 2C receptors in the spinal cord reduces pain transmission by lowering substance P release. In the present study, after extubation there was a considerable reduction in the post-operative VAS score in group D compared to group C in the initial 30 minutes only. Chilkoti et al found that only the first 15 minutes after shifting the patient to PACU showed a statistically significant reduction in the VAS values in group D compared to the group C, after which there was no significant difference in the VAS pain levels between the two groups.[9]

In this present study, there was no incidence of bradycardia or hypotension, which required intervention as Dexmedetomidine without bolus dose was used. The results are consistent with those of Parikh et al.[10] Also in the present study incidence of nausea and vomiting between the two groups was comparable. Since nausea and vomiting may be induced by high catecholamine concentrations, a decrease of sympathetic tone could explain the antiemetic effect of Dexmedetomidine. The results are consistent with the study conducted by Liang X et al.[11]

CONCLUSION

Laparoscopic Cholecystectomy is associated with surges in haemodynamic responses to laryngoscopy, intubation, pneumoperitoneum and extubation. A low dose Dexmedetomidine infusion administered @ 0.4 mcg/kg/hr without a prior bolus helps to combat these effects. Also it contributes to a lighter sedation without affecting extubation time, as well as a reduction in the postoperative analgesic requirements with no major adverse effects.

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