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Original Research Article

Haemodynamic effects of low dose Dexmedetomidine infusion in patients undergoing laparoscopic cholecystectomy –A randomized study

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Abstract: Laparoscopic surgery had several advantages over conventional surgery for the patient. Dexmedetomidine due to its distinct properties can be used as an anaesthetic adjuvant in the form of intravenous infusion. We studied the use of low dose dexmedetomidine infusion in laparoscopic surgery and its effect on hemodynamics, sedation scores and analgesic requirements. After the approval of the hospital ethics committee of Mahatma Gandhi Memorial Hospital Warangal, Telangana state 90 patients, aged 25 to 52 years, ASA grade I to II, and scheduled for laparoscopic cholecystectomy, were included in the study. Control Group C received normal saline0.9%, Group D1received dexmedetomidine 0.2 µg/kg/h and Group D2 received dexmedetomidine 0.4µg/kg/ h intravenously. There was no significant difference in preoperative hemodynamic parameters between the groups. In control Group significant haemodynamic stress response was seen following laryngoscopy, tracheal intubation, creation of pneumoperitoneum and extubation. Index medetomidine groups, the haemodynamic response were significantly attenuated. In addition, dexmedetomidine provides lighter sedation and reduces the post‑operative analgesic requirements without any significant adverse effects. Dexmedetomidine 0.4mcg/kg/h was significantly more effective than 0.2mcg/kg/h and control group.
Keywords: Laparoscopy, Cholecystectomy, Dexmedetomidine, Haemodynamic response, Analgesia.

INTRODUCTION

Laparoscopic surgery is minimally invasive technique potentially offers reduced operative time and morbidity, decreased hospital stay and earlier returns to normal activities, less pain and less postoperative ileus compared with the traditional open surgical procedures and gaining importance in general surgery.

Dexmedetomidine, a highly selective, specific, and potent α2 adreno-receptor agonist, had sedative, analgesic, and sympatholytic actions, along with supraspinal, spinal, and peripheral actions, anxiolytic property and without producing significant respiratory depression. Its sympatholytic effect had shown to decrease MAP and HR by reducing norepinephrine release. Dexmedetomidine also shown to decrease BIS value in the intra operative period when used as an adjuvant with other drugs given as continuous i.v. infusion .

Dexmedetomidine had a relatively high ratio of α_2/α_1-activity (1620:10) may result in more potent effects of sedation without unwanted cardiovascular effects from $\alpha_1$receptor activation. The half-life of dexmedetomidine was shorter which increases the likelihood that a continuous infusion of dexmedetomidine might be useful for sedation. Its use in large doses was complicated by hypertension from α_2 receptor-mediated vascular constriction.

The primary aim of this study was therefore, to evaluate the effects of low dose dexmedetomidine infusion on haemodynamic response to critical incidences like laryngoscopy, endotracheal intubation, creation of pneumoperitoneum and extubation in patients undergoing laparoscopic surgery. The secondary aims were to observe the effects on extubation time, sedation levels, post-operative analgesia requirements, and occurrence of adverse effects.

MATERIALS & METHODS

After the approval of the hospital ethics committee of Mahatma Gandhi Memorial Hospital,

Warangal, Telangana state 90 patients, aged 25 to 52 years, ASA (American Society of Anaesthesiologists) physical classification I to II, and scheduled for laparoscopic surgery, were included in the study. All patients signed a written informed consent form. Patients having an allergy to α_2 adrenergic agonist or sulpha drugs, uncontrolled hypertension, heart block, clinically significant neurologic, cardiovascular, renal, hepatic, or gastrointestinal diseases, pregnant or breast-feeding, and a history of alcohol or drug abuse were excluded in this study.

The patients were randomly assigned in to three treatment groups.
Group C: control group received normal saline0.9% i.v,
Group D1: received dexmedetomidine 0.2 μg/kg/h i.v,
Group D2: received dexmedetomidine0.4 μg/kg/h i.v.

Before surgery (24 h) the patients did not receive analgesics or sedatives. Upon arrival to the operating room, a 20-gauge cannula was inserted into the dorsum of the patient's hand and connected to a Connector for drug administration. Standard ASA monitors were attached, including non-invasive arterial pressure, electrocardiography, and pulse oximetry. All the patients were premedicated with intravascular injections of 50 mg ranitidine, ondensteron4mg and intra muscular 0.005 mg/kg glycopyrrolate, tramadol 1.0 mg/kg at least 1h before the surgery.

The study drug infusion kept at room temperature was prepared by an independent anaesthesiologist not involved in the study in a separate O.T. To prepare the infusion, dexmedetomidine 0.5 ml containing 50 mcg of the drug was withdrawn in a 20 ml. syringe and was diluted up to 12.5 ml with normal saline resulting in the final concentration of 4 mcg/ml. Dexmedetomidine or normal saline infusion was given through INFUSA® 101-P syringe infusion pump. Depending on the weight of the patient, the pump was set so as to deliver the targeted infusion rate.

Fifteen minutes after starting the drug infusion, pre-oxygenation was performed for 3 min. Anaesthesia was induced with midazolam 0.03 mg/kg, fentanyl 1.5mcg/kg and propofol 1-2 mg/kg body weight followed by vecuronium 0.15 mg/kg body weight. Trachea was intubated with appropriate size cuffed endotracheal tube. Anaesthesia was maintained with O2:N2O (50:50), sevoflurane and injection vecuronium bromide as a muscle relaxant. Intra‑abdominal pressure was maintained between 12 and 14 mmHg throughout the laparoscopic procedure. Ventilation was adjusted to maintain an end-tidal carbon dioxide ($ETCO_2$) value between 35 and 40 mm Hg. Drug infusion and anaesthetic agents were stopped at the end of surgery. Reversal was carried out. Patients were closely monitored throughout the intraoperative and immediate postoperative period.

All the patients were observed for vital parameters like Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded preoperative, after study drug administration, after induction, after intubation, after pneumoperitoneum at 15 min intervals, post pneumoperitoneum (PP) and after extubation. Patients were also observed for sedation level using Ramsay Sedation score, time to first rescue analgesic requirement, total amount of analgesic drug required during the first 24 h post‑operatively and the adverse effects.

Injection diclofenac sodium 1.5 mg/kg IM was used as rescue analgesia. Hypotension (MAP <20% preoperative) was managed with a fluid bolus of normal saline 250-300 ml. If hypotension did not respond to fluid administration, then inj. mephentermine 5 mg i.v. was administered. If hypotension did not respond to 2 repeat doses of mephentermine then dopamine infusion was started to maintain the blood pressure. Any incidence of bradycardia (HR < 50/min) was treated with inj. atropine 0.6 mg i.v. Hypertension (MAP >20% preoperative) was managed with nitroglycerine infusion.

The data collected were tabulated and analyzed by using the statistical package for social sciences, Windows-based version 16.0 (SPSS Inc., Chicago, IL, USA). The patients' characteristics were analyzed by using one-way analysis of variance (one-way ANOVA) and chi-square test was used for comparison of the categorical data.

RESULTS

There were no significant difference among the groups with respect to age, weight, height, sex, ASA grades, duration of surgery and duration of anaesthesia (table .1).

There was no significant difference in preoperative hemodynamic parameters between the groups. After administration of the study drugs, there was a significant decrease in heart rate(HR) and mean arterial pressure(MAP) in Group D1 and D2 ($p<0.01$) compared to the control group. After Intubation there was mild increase in HR and MAP in all the groups. Control group showed significant rise in HR& MAP during the pneumoperitoneum at different intervals but the D1&D2 groups recorded the significantly low HR& MAP when compared to preoperative readings($p<0.05$) however there was no significant difference within these intervals. After extubation, the HR&MAP increased significantly above the

pre‑ infusion level in Control group, though D1 &D2 groups remained below pre‑ infusion level (table 2).

Table-1: Demographic profile and duration of surgery

Variables	**Group C**	**Group D1**	**Group D2**
Age (Yrs.)	37.36±7.45	40.96±6.61	41.28±8.92
Weight (Kg)	54.38±7.24	51.24±9.32	53.76±4.28
Male/Female	10/20	14/16	13/17
Duration of surgery	74.26±17.36	79.42±16.41	66.33±18.21
Duration of anaesthesia	92.36±18.92	98.47±14.21	95.33±16.98

Values were expressed in Mean ± SD

Table 2: Heart rate and MAP at various time intervals in three groups

Time interval	heart rate (HR ,beats/min)			Mean arterial pressure (MAP, mm of Hg)		
	Group C	Group D1	Group D2	Group C	Group D1	Group D2
Pre operative	87.72±10.26	89.85±9.72	90.12±9.64	95.15±9.30	98.03±7.32	97.52±9.64
After Study Drug	85.12±9.28	81.69±9.62	81.26±9.31	94.21±9.64	96.59±8.59	95.82±6.32
After Induction	86.14±9.78	80.72±7.68*	81.04±8.36*	95.14±2.59	87.15±8.58*	86.24±9.82*
After Intubation	105.23±9.08*	99.89±6.42	86.23±8.12	108.92±8.32*	101.63±9.62	98.55±9.31
After pnuemoperitoneum						
a.15min	98.32±7.32*	82.42±7.61	78.64±7.91	105.04±7.91	96.21±9.81	89.50±7.61
b.30 min	97.62±6.21*	81.42±7.12	76.65±8.12	101.42±7.95	93.96±9.02	89.10.±7.91
c. 45min	96.92±9.13*	79.14±7.67	75.80±5.09	100.89±8.45	93.07±8.59	90.10±9.52
P 60min	92.15±8.09*	80.16±7.30	73.32±8.59	98.98±9.76	92.14±9.49	90.32±7.30
Post Pneumo peritoneum	89.92±8.37	78.00±10.56	75.05±4.36	95.92±8.36	90.24±7.55	90.03±9.19
after extubation	101.63±8.22*	77.38±9.32*	83.69±6.25*	112.89±7.32*	90.45±8.17*	88.59±7.62*

Values were expressed in Mean ±SD, p<0.05 Significant.

Systolic and Diastolic blood pressure values were statistically significantly lower in the D1 and D2 after induction, intubation and all time observations of pneumoperitoneum, when compared with the control group (p<0.001). In control there was a statistically significant increase after intubation and during pneumoperitoneum period, but this increase was less in group D1. In group D2 there was no statistically significant increase after intubation and slight decrease in time intervals of pneumoperitoneum were observed (table 3).

Table 3: Systolic and Diastolic blood pressure (mm of Hg) at various time intervals in three groups

Time interval	Systolic blood pressure			Diastolic blood pressure		
	Group C	Group D1	Group D2	Group C	Group D1	Group D2
Preoperative	126.86±8.35	123.96±10.70	123.89±8.95	78.14±9.09	79.66±9.76	78.45±7.02
After Study Drug	123.26±9.29	119.01±8.52*	114.28±9.42*	76.86±8.90	76.86±6.92	74.37±9.36*
After Induction	119.02±9.21*	113.99±6.55*	105.62±8.47*	73.98±6.51	72.67±8.86*	70.02±7.06*
After Intubation	149.07±9.36*	137.67±9.17*	123.52±6.35	96.07±7.61*	89.56±9.92*	80.06±7.21
After pneumoperitoneum						
a.15 min	145.39±8.75	134.98±6.52	118.96±8.51	91.94±9.32	87.16±7.87	79.81±8.34
b.30 min	143.98±9.28	133.02±7.65	120.42±6.29	89.68±5.14	84.02±4.26	74.92±8.26
c.45min	140.92±5.96	134.76±9.52	116.92±9.05	87.23±7.23	85.68±8.26	72.88±6.23
d.60 min	142.99±7.01	133.86±7.35	117.03±9.56	87.92±9.06	79.52±8.13	74.96±6.23
Post pneumoperitoneum	131.81±6.36	124.97±6.77	112.14±6.21	81.74±9.85	74.03±9.15	70.35±5.59
After extubation	127.07±8.15	122.24±9.45	114.38±9.53*	85.21±9.18	73.38±5.85	68.83±6.12*

Values were expressed in Mean ±SD, *p<0.05 is significant.

The mean sedation scores were less in control group compared to dexmedetomidine groups. D2 group patients had better sedation than D1 group patients. All patients in dexmedetomidine groups developed significant sedation levels and were cooperative, oriented and tranquil all the time. In control group sedation score improved subsequently due to early requirement of analgesic drugs.

All the patients in control group, 19 patients in group D1 and 8 patients in group D2 group required rescue analgesia. The analgesic needed in control after 62.23±5.26 min, compared to dexmedetomidine groups164.14±8.26 min in D1 and 262.45±6.21 min in D2 respectively.

Hypotension was observed in only one patient in D2, which responded to administration 1 dose of mephentermine 5 mg i.v and bradycardia was seen in 1 patient and treated with inj. atropine 0.6 mg i.v. Hypertension observed 5 patients of control and 3 patients of D1. Tachycardia observed in 6 members of control group and 3members of D1 group respectively. Hypertension was managed with nitroglycerine infusion.

DISCUSSION

The study was carried to know the safety and efficacy of small-dose dexmedetomidine infusion in patients undergoing laparoscopic surgeries by evaluating haemodynamic parameters, sedation and analgesia.

Laparoscopic surgical procedures have various benefits to the patient in terms of decreased tissue damage, early ambulation, decreased hospital stay, reduced analgesic needs. However creation of pneumoperitoneum has its own disadvantages in terms of adverse hemodynamic cardiovascular, respiratory, stress response and acid base physiology [1]. The increase in mean arterial pressure (MAP) and systemic vascular resistance (SVR) occurring immediately at the induction of pneumoperitoneum is suggestive of involvement of the sympathetic nervous system [2]. These hemodynamic responses are due to increased release of catecholamines, vasopressin, or both [3, 4]. To control and modify of these hemodynamic changes many technique have been tried to attenuate these responses. Various pharmacological agents were used. One of these drugs dexmedetomidine used to provide hemodynamic stability during pneumoperitoneum with varying success rate [5, 6].

Dexmedetomidine was a highly selective α2 adrenergic agonist. It acts through three types of α2 receptors - α2A,α2B and α2C situated in brain and spinal cord. The resultant action was sedation, anxiolysis, analgesia and sympatholysis, the latter leading to hypotension and bradycardia. Activation of α2 A receptors in brainstem vasomotor centre results in suppression of norepinephrine release, hypotension and bradycardia. Stimulation of α2A and α2C in locus ceruleus causes sedation. In the spinal cord, activation of both α2A and α2C receptors directly reduce pain transmission by reducing release of substance P [6]. Dexmedetomidine modulates the hemodynamic changes induced by pneumoperitoneum by inhibiting the release of catecholamines and vasopressin [7].

Dexmedetomidine Infusion rates varying from 0.1 to 10 mcg/kg/h [8,9,10] have been studied. Low dose infusion of 0.25–0.5 mcg/kg/h results in a monophasic response of 10–15% fall in mean arterial blood pressure and PR[11] However, with higher dose infusion of dexmedetomidine, high incidence of adverse cardiac effects have been observed[10]. This study confirms that 0.4 mcg/kg/h infusion dose was effective in maintaining haemodynamic stability with minimum side effects [6].

Dexmedetomidine had significant sympatholytic and haemodynamic stability property. It causes dose-dependent decrease in heart rate and blood pressure. Earlier studies have shown that dexmedetomidine attenuates stress response to intubation by decreasing central sympathetic outflow, thereby decreasing serum epinephrine and norepinephrine levels. This study confirms that significant increase the MAP and PR in patients undergoing laparoscopic surgeries observed at critical points like laryngoscopy and intubation, pneumoperitoneum and extubation [12, 13&14]. Dexmedetomidine when compared with conventional sedatives and opiates has been demonstrated to be associated with both sedative and analgesic effects, reduced delirium and agitation, minimal respiratory depression and predictable and desirable cardiovascular effects. Central nervous system stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus coeruleus inthe brainstem plays a prominent role in sedation and anxiolysis. Decreased noradrenergic output from the locus coeruleus allows increased firing of inhibitory neuron (GABA). The patients can be easily aroused to cooperate during procedures and also respond to the verbal commands and then can return to sleep like state when not stimulated. Sedation is dose dependent and reaches its peak after 45–60min [15]. Sedation decreases gradually after stopping the infusion [16]. In our study sedation scores were more in D2, less in D1, very less in control group.

Primary analgesic effects of dexmedetomidine result from the activation of the a2 adrenergic receptor in the dorsal horn of the spinal cord and inhibition of substance P release. In this study time for analgesic

requirement was increased significantly compared to the control and quantity of analgesic requirement also decreased significantly [6&17]. This study reports that 92% of the patient son dexmedetomidine infusions were easily weaned and extubated like the other previous studies [6&17].

CONCLUSION:

This study confirms that low dose infusion of dexmedetomidine effectively attenuates haemodynamic stress response to intubation, pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy. In addition, dexmedetomidine provides lighter sedation and reduces the post‑operative analgesic requirements without any significant adverse effects. Dexmedetomidine 0.4mcg/kg/h is significantly more effective than 0.2mcg/kg/h.

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