Clinical Investigation

Effects of low dose dexmedetomidine infusion on haemodynamic stress response, sedation and post-operative analgesia requirement in patients undergoing laparoscopic cholecystectomy

Address for correspondence:
Dr. Gourishankar Reddy Manne,
C/o Dr Hasreddy Manne.
Plot No 24, Narasimha Nilaya,
Vidya Nagar, Sedam,
Gulbarga - 585 222,
Karnataka, India.
E-mail: gaurishviz010@gmail.com

Gourishankar Reddy Manne, Mahendra R Upadhyay, VN Swadia
Department of Anaesthesiology, Medical College, Vadodara, Gujarat, India

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ABSTRACT

Background and Aim: Dexmedetomidine is a α2 agonist with sedative, sympatholytic and analgesic properties and hence, it can be a very useful adjuvant in anaesthesia as stress response buster, sedative and analgesic. We aimed primarily to evaluate the effects of low dose dexmedetomidine infusion on haemodynamic response to critical incidences such as laryngoscopy, endotracheal intubation, creation of pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy. The secondary aims were to observe the effects on extubation time, sedation levels, post-operative analgesia requirements and occurrence of adverse effects. **Methods:** Sixty patients of American Society of Anaesthesiologists(ASA) physical grades I and II undergoing laparoscopic cholecystectomy were randomly allocated into three groups of 20 patients each. Group NS patients received normal saline, Group Dex 0.2 and Group Dex 0.4 patients received dexmedetomidine infusion at 0.2 mcg/kg/h and 0.4 mcg/kg/h respectively, starting 15 min before induction and continued till end of surgery. Parameters noted were pulse rate, mean arterial pressure, oxygen saturation, post-operative sedation and analgesia requirements. SPSS 15.0 version software was used for statistical analysis. ANOVA test for continuous variables, *post-hoc* test for intergroup comparison, and Chi-square test for discrete values were applied. **Results:** In Group NS significant haemodynamic stress response was seen following laryngoscopy, tracheal intubation, creation of pneumoperitoneum and extubation. In dexmedetomidine groups, the haemodynamic response was significantly attenuated. The results, however, were statistically better in Dex 0.4 group compared with Dex 0.2 group. Post-operative 24 hour analgesic requirements were much less in dexmedetomidine groups. No significant side effects were noted. **Conclusion:** Low dose dexmedetomidine infusion in the dose of 0.4 mcg/kg/h effectively attenuates haemodynamic stress response during laparoscopic surgery with reduction in post-operative analgesic requirements.

Key words: Dexmedetomidine, haemodynamic stress response, laparoscopic cholecystectomy

INTRODUCTION

Laparoscopic cholecystectomy is one of the most commonly practiced surgeries for gall bladder diseases in the present era. Due to its well-known advantages like less post-operative pain, shorter hospitalization and faster functional recovery, laparoscopic cholecystectomy is also termed as patient friendly surgery. However, like any other surgery, laparoscopic cholecystectomy is also associated with stress response induced by surgery and anaesthesia.

Anaesthetic manoeuvres like direct laryngoscopy, tracheal intubation and extubation involve severe sympathetic stimulation. Moreover, the pneumoperitoneum and carbon dioxide insufflations,

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required in laparoscopic surgeries, lead to Increase in plasma nor-epinephrine, epinephrine levels and plasma renin activity.[1] All these changes lead to increase in heart rate, blood pressure, systemic and pulmonary vascular resistance, and reduced cardiac output. The reverse Trendelenburg position required for surgery leads to diminished venous return and thereby, further reduction in cardiac output.[2] The haemodynamic changes predispose the myocardium to ischemia that may be life threatening in a vulnerable patient.

Modern anaesthesia practices, therefore, plan to prevent sympathetic discharge and provide haemodynamic stability perioperatively. Various agents in the form of opioid analgesics, benzodiazepines, beta blockers, calcium channel blockers and vasodilators have been used to achieve this objective with variable success. In last few years, a great enthusiasm has been shown toward the use of α2 agonists in anaesthesia practice because of their anxiolytic, sedative, sympatholytic and analgesic sparing properties.[3]

Dexmedetomidine, introduced in 1999 for human use, is a selective α2 agonist with 8 times more affinity for α2 adrenergic receptors compared to clonidine and possesses all the properties of α2 agonist without respiratory depression.[4,5] Intravenous use of dexmedetomidine in the perioperative period had been found to decrease serum catecholamine levels by 90%,[6] to blunt the haemodynamic response to laryngoscopy, tracheal intubation, pneumoperitoneum and extubation,[7] to provide sedation without respiratory depression[4] and to decrease post-operative analgesic requirements.[8]

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 cholecystectomy. The secondary aims were to observe the effects on extubation time, sedation levels, post-operative analgesia requirements, and occurrence of adverse effects.

METHODS

The present study was carried out from August 2010 to July 2012, after taking the permission and approval from the Departmental Ethical Committee and the written informed consent from the patients. It was a prospective, randomised, double blind, placebo controlled clinical study. Sixty ASA physical grades I and II patients between 18 and 65 years, of either sex and posted for laparoscopic cholecystectomy under general anaesthesia were included in the study. Patients with decreased autonomic control such as the elderly, diabetic patients, patients with chronic hypertension or severe cardiac disease, patients on drugs like β blockers or calcium channel blockers, pregnant or lactating women, patients with history of allergy to egg proteins and drugs particularly α2 agonists were not considered for the study.

The patients were randomly allocated by envelope method into three groups of 20 patients each, Group NS (patients receiving normal saline 0.9% infusion), Group Dex 0.2 (patients receiving dexmeditomidine infusion 0.2 mcg/kg/h) and Group Dex 0.4 (patients receiving dexmedetomidine infusion 0.4 mcg/kg/h).

Infusion was prepared according to the group allotted in a separate O.T. To prepare the infusion, dexmedetomidine 0.5 ml containing 50 μg 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. After the setting the infusion pump, it was covered with blue cloth so that the assessor did not come to know about the grouping of the patient. Thus, the syringe was same, volume of prepared solution was same, only the rate of injection was different according to the weight and group of patient. Thus, the assessor and the patient were unaware of the group. Decoding of blinding to the assessor was done only at the time of tabulation and result analysis.

After taking the patient on the operation table, a multipara monitor was attached and the baseline pulse rate (PR), mean arterial pressure (MAP) and oxygen saturation were noted down. A wide bore intravenous cannula was inserted for giving the intravenous fluids, and another line was taken up for the infusion pump. Premedication was administered 45 min before induction of anaesthesia to all the patients in the form of injection glycopyrrolate 5 mcg/kg IM and injection tramadol 1.0 mg/kg IM as per the institutional protocol. At the time of induction, all the patients

received injection ranitidine 50 mg IV and injection ondansetron 4 mg IV.

Fifteen minutes after starting the drug infusion, pre-oxygenation was performed for 3 min. Patients were induced with injection propofol 2 mg/kg intravenously followed by injection succinyl choline 1.5 mg/kg intravenously. Trachea was intubated with appropriate size cuffed endotracheal tube. Anaesthesia was maintained with O_2:N_2O (50:50), isoflurane and injection vecuronium bromide as a muscle relaxant on Fabius Plus® work station. Intra-abdominal pressure was maintained between 12 and 14 mmHg throughout the laparoscopic procedure. The patients were mechanically ventilated using circle system to keep the $EtCO_2$ between 35 and 45 mm Hg. Drug infusion and anaesthetic agents were stopped at the end of surgery. Reversal was carried out as also extubation by conventional methods.

All the patients were observed for vital parameters like PR, MAP and SpO_2 at regular intervals including before starting the infusion, 15 min after starting the infusion, after induction, after intubation, after creation and release of pneumoperitoneum and after extubation. Patients were also observed for time to extubate trachea, post-operative sedation level, time to first rescue analgesic requirement (time from completion of injection of drug to the time post- operatively, when pain reported by patient was ≥ 4 on visual analogue scale [VAS], 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 analgesic and thereafter whenever the VAS score became ≥4.

Extubation time was counted from stoppage of anaesthetic agent to time, when the extubation was done. Sedation was assessed at 1, 15, 30, 60 to 120 min post-operatively using Ramsay sedation score (RSS). Throughout the study, patients were observed for any adverse effects like bradycardia, tachycardia (PR less than or more than 20% of pre-operative level respectively on two consecutive readings), hypo and hypertension (MAP less than or more than 20% of pre-operative level respectively on two consecutive readings), sedation score more than RSS 4, respiratory depression (SaO_2 < 90%) and dryness of mouth and they were managed conventionally.

Sample size was calculated using MedCalc Software version 11.5.0.0. (MedCalc Software bvba, Acacialaan 22, 8400 Ostend, Belgium) Based on minimum mean difference of 25% in parameters with $\alpha = 0.01$ and $\beta = 0.20$, sample size for each group was estimated as 18. Rounding up this figure, we took 20 patients in each group. The results were tabulated and statistically analysed using SPSS (Statistical Package for Social Sciences) Software version 15.0, Chi-square test was used for qualitative data (sex, ASA grade), PR, blood pressure, oxygen saturation, end tidal carbon dioxide etc., were compared within the group against baseline values using paired *t*-test. ANOVA test was used for three group comparisons of continuous variables; if ANOVA was found significant, tuckey *post-hoc* test was used for comparing two groups and the results were expressed as mean ± standard deviation. $P > 0.05$ was considered insignificant, < 0.05 as significant and highly significant if < 0.001.

RESULTS

All the three groups under study were comparable to each other with respect to age, sex, weight, ASA grading, duration of surgery and anaesthesia [Table 1]. There was no significant difference among the three groups in reference to the baseline PR and the MAP.

In group NS, after starting the infusion there was no significant change in PR and MAP but these increased highly significantly above pre-infusion level after intubation and extubation ($P < 0.01$) and significantly after pneumoperitoneum [$P < 0.05$, Tables 2 and 3].

In both the dexmedetomidine groups, after starting the infusion, the PR decreased highly significantly below the pre-infusion level. The MAP decreased significantly in Dex 0.2 group and highly significantly in Dex 0.4 group. No further significant changes were observed immediately after induction. After intubation and extubation, the PR and MAP increased significantly above the pre-infusion level in Dex 0.2 group, though, this increase was less compared to increase in group NS ($P < 0.05$). Unlike these changes in Dex 0.2 group, PR and MAP in Dex 0.4 group remained below pre-infusion level after intubation and extubation ($P < 0.05$ when compared with Dex 0.02). Pneumoperitoneum did not produce a significant effect in both the Dex groups.

The mean sedation scores [Table 4] were more in dexmedetomidine groups compared to normal saline group patients. Dex 0.4 group patients had better sedation than Dex 0.2 group patients. None of the patients in dexmedetomidine groups developed

Table 1: Demographic characteristics and duration of surgery and anaesthesia

Parameters	Group NS (%)	Group Dex 0.2 (%)	Group Dex 0.4 (%)	Intergroup *P*
Age in years (mean±SD and range)	41.25±7.38 (26-54)	40.05±10.33 (23-59)	42.05±7.72 (30-60)	
Sex				
Male	3 (15)	7 (35)	6 (30)	
Female	17 (85)	13 (65)	14 (70)	
Weight in kg (mean±SD and range)	55.25±8.48 (44-68)	55.95±6.36 (45-69)	53.65±6.31 (42-66)	
ASA				
1	19 (95)	18 (90)	19 (95)	>0.05
2	1 (5)	2 (10)	1 (5)	
Duration of anaesthesia (in min)	93.55±21.960	99.05±37.347	84.05±31.405	>0.05
Duration of surgery (in min)	76.80±21.824	91.15±34.223	74.05±25.527	>0.05

SD – Standard deviation; NS – Normal saline; Dex – Dexmedetomidine; ASA – American Society of Anesthesiologist

Table 2: Changes in PR (beats per minute) (mean±SD)

Time	Group NS	Group Dex 0.2	Group Dex 0.4
Before starting infusion	88.75±5.71	91.90±8.66	90.75±8.42
15 min after starting infusion	87.50±3.61	82.05±5.84††	80.65±7.15††
1 min after induction	86.50±3.80	82.90±8.95††	80.55±9.05††
After laryngoscopy and intubation			
1 min	106.25±5.16**	99.30±4.66*	87.15±8.23†
After pneumoperitoneum			
1 min	93.75±4.80*	82.60±5.04	78.60±9.91
15 min	91.65±5.88	79.90±5.63	76.65±11.01
30 min	90.15±5.12	79.85±5.66	76.70±10.58
45 min	88.05±4.43	80.56±5.83	77.18±10.69
60 min	88.38±6.47	77.71±7.84	75.71±9.47
After release of pneumoperitoneum			
1 min	85.60±3.40	76.75±4.04	76.05±8.45
After extubation			
1 min	102.15±7.35**	92.45±9.42	83.95±9.57

*Significant rise; **Highly significant rise; †Significant fall; ††Highly significant fall. PR – Pulse rate; SD – Standard deviation; NS – Normal saline; Dex – Dexmedetomidine

Table 3: Changes in MAP (mm of Hg) (mean±SD)

Time	Group NS	Group Dex (0.2)	Group Dex (0.4)
Before starting infusion	99.40±9.714	99.30±11.549	101.50±4.95
15 min after starting infusion	98.65±4.727	95.45±9.310†	93.05±6.41††
1 min after induction	98.90±5.370	89.80±8.721††	89.55±5.66††
After laryngoscopy and intubation			
1 min	114.35±13.120**	103.85±12.132*	95.65±6.59
After pneumoperitoneum			
1 min	102.65±9.97*	94.85±11.375	89.50±9.33
15 min	100.30±10.301	96.95±10.278	91.40±10.10
30 min	95.10±7.440	94.05±10.430	91.70±8.79
45 min	96.85±8.647	93.83±12.349	90.82±8.51
60 min	95.81±9.614	95.76±10.923	90.93±10.62
After release of pneumoperitoneum			
1 min	95.00±8.079	93.30±11.784	88.15±9.42
After extubation			
1 min	114.65±10.075**	106.35±12.453*	98.30±6.82

*Significant rise; **Highly significant rise; †Significant fall; ††Highly significant fall. NS – Normal saline; Dex – Dexmedetomidine; MAP – Mean arterial pressure; SD – Standard deviation

siginificant sedation levels and the patients were cooperative, oriented and tranquil all the time. In group NS sedation score, which was less initially, improved subsequently due to early requirement of analgesia in this group.

There was no significant difference among the three groups with reference to extubation time (7.15 ± 1.20, 6.55 ± 1.27 and 6.40 ± 1.04 min in group NS, Dex 0.2 and Dex 0.4 group respectively.

The rescue analgesia was required early (55.5 min.) in Group NS compared to dexmedetomidine groups (173 min in Dex 0.2 and 249 min in Dex 0.4 group). All the patients in group NS, 15 patients in group Dex 0.2 and 10 patients in group Dex 0.4 group required rescue analgesia. Total analgesic requirement of first 24 h post-operative period also decreased by 36.11% in group Dex 0.2 and by 63.88% in Group Dex 0.4 [Table 5].

Tachycardia and hypertension were seen in 7 and 6 patients of Group NS compared to 1 and 2 patients of group Dex 0.2. Hypotension was noted in 1 patient of group Dex 0.2 and bradycardia was seen in 1 patient of Dex 0.4 group.

DISCUSSION

Dexmedetomidine is a highly selective α2 adrenergic agonist. It acts through three types of α2 receptors-α2 A, α2 B and α2 C situated in brain and spinal cord. The resultant action is sedation, anxiolysis, analgesia and

Table 4: Changes in mean sedation score

Group	Post-operative (mean±SD)					
	1 min	15 min	30 min	45 min	60 min	120 min
Group NS	1.25±0.40	1.45±0.51	1.7±0.40	1.80±0.30	1.85±0.25	1.85±0.24
Group Dex 0.2	2.05±0.54	1.85±0.40	1.95±0.18	2.0±0.10	2.05±0.09	2.05±0.09
Group Dex 0.4	2.80±0.35	2.45±0.09	2.26±0.36	2.05±0.09	2.21±0.31	2.10±0.17

SD – Standard deviation; NS – Normal saline; Dex – Dexmedetomidine

Table 5: Post-operative analgesic requirements

Group	Time for first rescue analgesic requirement (in min)	Cumulative analgesia required in 24 h (in mg)
Group NS	55.50	180.00 mg
Group Dex 0.2	173 (5 patients did not require any analgesia in first 24 h)	115 (10 patients did not require any analgesia in first 24 h)
Group Dex 0.4	249	97.5

NS – Normal saline; Dex – Dexmedetomidine

sympatholysis, the latter leading to hypotension and bradycardia. Activation of α2 A receptors in brain stem vasomotor centre results in suppression of norepinephrine release, hypotension and bradycardia. Stimulation of α2 A and α2 C in locus ceruleus causes sedation. In the spinal cord, activation of both α2 A and α2 C receptors directly reduce pain transmission by reducing release of substance P.

Looking at these pharmacological properties, it has been evaluated in the past to assess its effect on haemodynamic responses in patients undergoing laparoscopic surgeries. The molecule has been used in infusion form with or without bolus dose. Infusion rates varying from 0.1 to 10 mcg/kg/h[9,10,11] have been studied. However, with higher dose infusion of dexmedetomidine, high incidence of adverse cardiac effects have been observed.[11] A biphasic response on blood pressure occurs with a bolus dose.[6] Initially, there occurs hypertension followed by fall in blood pressure. This response is seen often more in young and healthy patients.[12] Stimulation of α2 B receptors in vascular smooth muscles is said to be responsible for this.

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.[6] Furthermore, in low dose, dexmedetomidine exhibits linear kinetics, meaning that a constant amount of drug is eliminated per hour rather than a constant fraction of drug.

Hence, in a pilot study, we used low dose infusions of dexmedetomidine without any bolus. Initially, we used dexmedetomidine 0.2 mcg/kg/h infusion. Though it controlled the rise in PR and MAP at pneumoperitoneum, the control was not very effective at the time of tracheal intubation and extubation, and the PR and MAP both increased above pre-infusion levels. Hence, we increased the dose to 0.4 mcg/kg/h infusion in our next two patients. The results were quite satisfactory with this dose regime. PR and MAP were always below pre-infusion levels in Dex 0.4 group. We also studied few cases with Dex 0.6 mcg/kg/h dose but the hypotension was seen in greater number of patients, and the sedation was more (RSS 4–5). Hence, we decided to have three groups in our study, which were Group NS, Group Dex 0.2 and Group Dex 0.4.

Our study confirms the fact that critical incidences like laryngoscopy and intubation, pneumoperitoneum and extubation do significantly increase the MAP and PR in patients undergoing laparoscopic cholecystectomy[1,14] as seen in group NS. Dexmedetomidine attenuates this sympathoadrenal response and provides haemodynamic stability.[13,14] The effective attenuation dose with minimum side effects noted in our study was 0.4 mcg/kg/h infusion.

Apart from providing stress response attenuation, the added effects of dexmedetomidine are sedation and analgesia. Sedation produced by α2 agonists is unique in the sense that the patients can be easily aroused to co-operate during procedures and also respond to the verbal commands and then can return to sleep like state when not stimulated.[12] Sedation is dose-dependent and reaches its peak after 45–60 min.[15] Sedation decreases gradually after stopping the infusion. We observed patients for 120 min as elimination half-life of dexmedetomidine is 2 h. Initially, the sedation score was more in Group Dex 0.4 compared to Group NS or Group Dex 0.2. Over a period of time mean sedation score settled around '2' in Group Dex 0.2 and Group Dex 0.4, while in Group NS, score improved from 1 to 2 because of early administration of analgesia 30–40 min post-operatively.

It may be hypothesised that due to its sedative effect, response to verbal command and extubation time may be delayed with dexmedetomidine. However, in our study

the mean extubation time did not show any significant difference between three groups. Bhattacharjee *et al*.[13] also observed no significant effect of dexmedetomidine on response to verbal command and extubation time.

Dexmedetomidine has been found to reduce the intra and post-operative requirement of opioids.[8,11,16,17] This effect of dexmedetomidine is classically described as opioid sparing effect. We also observed an increase in the time to receive first rescue analgesia and a decrease in total analgesic requirements in first 24 h post-operatively in both dexmedetomidine groups.

CONCLUSION

Low dose infusion of dexmedetomidine at the rate of 0.4 mcg/kg/h without any bolus dose serves as a very useful anaesthesia adjuvant to control haemodynamic stress response to intubation, pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy. It also provides lighter sedation and reduces the post-operative analgesic requirements without any significant adverse effects.

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