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Effects of Dexmedetomidine Infusion in different Concentrations on Intraoperative and Postoperative Hemodynamic Response and Analgesic Requirement in Laparoscopic Cholecystectomy Patients

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Abstract

Background: Dexmedetomidine is a newer α2 agonist with sedative, sympatholytic and analgesic properties. This study was carried out to evaluate the effect of two different concentrations of intravenous dexmedetomidine infusion on haemodynamic response to critical incidents like laryngoscopy, endotracheal intubation, creation of pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy. *Methods:* The study was conducted at our institute in 60 ASA grade I & II patients undergoing laparoscopic cholecystectomy. They were randomly allocated into two groups of 30 patients each 'Group Dex 0.25' and 'Group Dex 0.5'. The patients received dexmedetomidine infusion at the rate of 0.25 /kg/hr and 0.5 mcg/kg/hr respectively, starting 15 minutes before induction and continued till the end of surgery. Standard anaesthesia technique was used. Comparison of the effect of infusion on haemodynamic changes seen in laparoscopic cholecystectomy was done. *Results:* Haemodynamic response to laryngoscopy and creation of pneumoperitoneum was blunted more in group Dex 0.5 as compared to group Dex 0.25. The intraoperative and post operative analgesic requirement was also reduced in group Dex 0.5. The time to first analgesic demand was later in the group Dex 0.5 as against group Dex 0.25. No significant side effects were noted in either group. *Conclusion:* Dexmedetomidine infusion at the rate of 0.5 mcg/kg/hr given perioperatively can serve as a very useful anaesthetic adjunct for premedication, maintenance of haemodynamic stability and postoperative analgesia without any significant adverse effects.

Keywords: Dexmedetomidine; Laparoscopic cholecystectomy; Hemodynamics.

Introduction

Laparoscopic cholecystectomy is one of the most commonly practiced surgeries for gall bladder diseases in today`s era. However, like any other surgery, laparoscopic cholecystectomy is also associated with haemodynamic stress induced by surgery and anaesthesia, the two leading to an endocrine response starting adrenaline and nor adrenaline secretion by stimulation of sympathetic

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nervous system [1]. Anesthetic maneuvers like direct laryngoscopy, tracheal intubation and even extubation involve severe sympathetic stimulation leading to increase in serum catecholamine and nor epinephrine levels [2].

All these changes lead to increased blood pressure and heart rate, increased systemic and pulmonary vascular resistance and reduced cardiac output [3]. The reverse Trendelenberg position leads to diminished venous return and thereby further reduction in cardiac output [4]. The hyperdynamic changes predispose the myocardium to ischemia especially in the patient population with decreased reserve for coronary blood flow. Perioperative ischemia is associated with a significant increase in postoperative morbidity and mortality.

Modern anaesthesia practices aim 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 attenuate this stress response and to provide haemodynamic stability with variable success [1,2].

Several clinical studies suggest that α2 adrenergic agonists might be effective in blunting the perioperative haemodynamic response. Intravenous use of Dexmedetomidine in the intraoperative period decreases catecholamine by ninety percent, blunts the haemodynamic response to laryngoscopy, tracheal intubation, pneumoperitoneum and extubation, increases the haemodynamic stability, and decreases anaesthetic requirements and post operative analgesic requirements [2]. The analgesic, sedative, hypnotic and anxiolytic properties of dexmedetomidine make this drug potentially useful for painful surgical procedures.

Low dose infusion of 0.25–0.5 μg kg^{-1} hr^{-1} results in a monophasic response of 10-15% fall in mean arterial blood pressure and pulse rate. Furthermore, in low dose, dexmedetomidine exhibits linear kinetics, meaning that a constant amount of drug is eliminated per hour rather than a constant fraction.

In this study, we evaluated the effect of two different doses of Dexmedetomidine infusion (0.25 μg kg^{-1} and 0.5μg kg^{-1}) on haemodynamic response to various critical incidences like laryngoscopy, intubation, pneumoperitoneum and extubation and analgesic requirements in patients undergoing laparoscopic cholecystectomy. We hypothesise that dexmedetomidine infusion 0.5 μg/kg/hr provides better haemodynamic profile but may have increased incidence of side effects.

Material and Methods

This study was conducted with due approval by the Hospital ethics committee. Sixty ASA physical grades I and II patients between 18 and 65 years, of either sex and scheduled for laparoscopic cholecystectomy under general anaesthesia were enrolled in study and written informed consent was taken. Exclusion criteria were allergy to dexmedetomidine, respiratory disease, severe cardiovascular disease and BMI > 35 kg $m^{-2.}$

It was a prospective, randomized, comparative study carried out from February 2015 to November 2015.

A thorough preoperative evaluation of each patient was done. All patients were explained about the anaesthetic technique and perioperative course. All routine biochemical, hematological and radiological investigations were done.

Routine preoperative preparation consisted of fasting for 6-8 hours prior to surgery. All the patients were premedicated with tablet alprazolam 0.5 mg night before surgery.

At the time of this check up they were acquainted with the Visual analogue scale (VAS) for pain scoring.

All the monitoring was done on anesthesia work station Datex-Ohmeda with IntelliVue MP20 monitor calibrated to measure all hemodynamic parameters required for the study. The parameters monitored included heart rate and rhythm by three lead ECG, noninvasive blood pressure (systolic, diastolic and mean arterial pressure), oxygen saturation, end tidal concentrations of anesthetic agents and CO_2 level by capnograph and temperature monitoring.

The patients were allocated into two groups of 30 patients each, Group Dex 0.25 (patients receiving dexmedetomidine infusion 0.25 μg/kg/h) and Dex 0.5 (patients receiving dexmedetomidine infusion 0.5 μg/kg/h) based on a computer generated method.

A suitable size intravenous cannula was secured for intravenous fluids, and another line for drug infusion. Ringer Lactate was started @ 4 ml kg^{-1} hr^{-1}. Test drug infusion was started via infusion pump at the predetermined rate, according to the allocated group. The infusion was continued till the removal of scope from the abdominal cavity. Fifteen minutes after starting the drug infusion; patients were given midazolam 1 mg intravenous as premedication. After preoxygenation, induction was done with

Fentanyl 2.0 μg kg^{-1} body weight intravenously and Propofol 2 mg kg^{-1} body weight intravenously. Vecuronium bromide 0.1 mg kg^{-1} body weight intravenously was used for intubation. Anaesthesia was maintained with Isoflurane and Nitrous oxide in oxygen and vecuronium bromide with controlled ventilation using circle system maintaining a MAC of 1.2. Intraabdominal pressure was maintained between 12 and 14 mmHg throughout the procedure. During maintenance of anesthesia, administration of Fentanyl 0.5 to 1 μg kg^{-1} body weight was added depending upon clinical condition and alteration of hemodynamic parameters (tachycardia and hypertension). Drug infusion and anaesthetic agents were stopped at the end of surgery, as soon as the scope was taken out of the abdominal cavity. Neuromuscular blockade was reversed with Neostigmine (0.04 mg kg^{-1}) and Glycopyrrolate (0.01 mg kg^{-1}). At the end of the surgery all patients were given Ondansetron 4 mg for prevention of post operative nausea and vomiting.

Vital parameters were observed at regular intervals including before starting the infusion, 10 minutes after starting the infusion, after induction, after creation and release of pneumoperitoneum and after extubation.

After surgery, the following parameters were recorded every hour for the first 6 hours and then at 12 hours and 24 hours post operatively in the ward - heart rate, mean blood pressure (MBP), oxygen saturation, time to first analgesic demand, VAS and total post operative analgesic requirement. Sedation was assessed at 1, 15, 30, 60 to 120 minutes after extubation using Ramsay sedation score (RSS).

When pain reported by patient was ≥ 4 on visual analogue scale [VAS], Injection diclofenac sodium 1.5 mg kg^{-1} intramuscular was used as rescue analgesic and repeated thereafter whenever the VAS score became ≥4.

Throughout the study, patients were observed for any adverse effects like bradycardia, tachycardia (PR less than or more than 20% of preoperative level respectively on two consecutive readings), hypo and hypertension (MBP less than or more than 20% of preoperative 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.

Statistics

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 (mean heart rate and mean blood pressure) with α =0.01 and β =0.20, sample size for each group was estimated as 28. Rounding up this figure, a sample size of 30 per group was required to detect a significant difference between the groups.

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), heart rate, Mean blood pressure, were compared within the group against baseline values using paired *t*test. p >0.05 was considered insignificant, p<0.05 as significant and highly significant if p<0.001.

Results

Both groups were comparable in terms of age, weight, sex, ASA grade distribution and duration of surgery as shown in table 1.

The mean baseline variables (HR, SBP, DBP, MBP, SpO_2) were comparable in both groups.

On Comparison, the mean heart rate and the mean blood pressure at initiation of the drug infusion decreased significantly from the base line value in both the groups, the fall being more in the DEX 0.5 group. Thereafter the mean heart rate and mean blood pressure in the DEX 0.5 group was less than that in DEX 0.25 group at all the above mentioned time points. The difference being statistically significant as shown in table 2 and table 3. Also the mean heart rate and mean blood pressure post operatively in the post anaesthesia care unit in the DEX 0.5 group was less than the mean heart rate and mean blood pressure in DEX 0.25 group at all the above mentioned time points (Table 4).

None of the patients in either group had significant bradycardia or hypotension, requiring a rescue medication.

In our study fentanyl citrate top-ups of

Table 1: Demographic data

	Group DEX 0.25 (n =30)	Group DEX 0.5 (n =30)
Age (yrs)	39.2 ± 8.6	39.2 ± 8.8
Sex (M/F)	21/9	20/10
Height (cms)	159.2 ± 6.3	158.3 ± 6.3
Weight (kg)	63.5 ± 5.4	60.43 ± 7.5
ASA (I/II)	21/9	20/10
Duration of surgery (mins)	73.5 ± 18.5	69.3 ± 19.3

Table 2: Mean Intra Operative Heart Rate (BPM) in the two Groups

Time	Group Dex 0.25 Mean SD	Group Dex 0.5 Mean ± SD	Inter group p value
Before starting infusion	87.4 ± 9.45	91.53 ± 10.66	0.1323
10 min after starting infusion	82.3 ± 7.44	72.8 ± 3.15	< 0.0001
1 min after Induction	77.33 ± 14.29	67.8 ± 4.65	< 0.0001
1 min after Intubation	83.463 ± 3.10	73.13 ± 8.57	< 0.0001
5 min after Intubation	83.93 ± 3.70	75.13 ± 5.78	< 0.0001
1 min after Pneumoperitoneum	85.36 ± 1.96	78.26 ± 6.92	< 0.0001
15 min after Pneumoperitoneum	86.8 ± 5.98	77.8 ± 6.44	< 0.0001
30 min after Pneumoperitoneum	86.6 ± 3.68	77.9 ± 7.43	< 0.0001
45 min after Pneumoperitoneum	84.1 ± 4.87	75.3 ± 7.58	< 0.0001
60 min after Pneumoperitoneum	84.53 ± 7.14	76.43 ± 7.06	< 0.0001
1 min after Release of pneumoperitoneum	81.9 ± 5.80	74.9 ± 6.46	< 0.0001
15 min after Release of pneumoperitoneum	82.36 ± 4.94	75.9 ± 5.30	< 0.0001
After extubation	87.9 ± 4.47	77.06 ± 4.4	< 0.0001

Table 3: Mean Intra Operative Mean Blood Pressure in the two Groups (mmHg)

Time	Group Dex 0.25 Mean ± SD	Group Dex 0.5 Mean ± SD	Inter group P value
Before starting infusion	93.46 ± 5.02	93.83 ± 4.10	0.0195
10 min after starting infusion	87.5 ± 5.48	75.2 ± 3.43	0.3445
1 min after Induction	83.47 ± 5.66	71.03 ± 4.78	< 0.0001
1 min after Intubation	85.03 ± 3.45	73.3 ± 12.48	<0.001
5 min after Intubation	84.97 ± 3.42	73.93 ± 2.52	<0.001
1 min after Pneumoperitoneum	86.07 ± 14.81	75.7 ± 2.08	<0.001
15 min after Pneumoperitoneum	86.43 ± 2.06	76.4 ± 3.05	< 0.0001
30 min after Pneumoperitoneum	86.33 ± 2.61	75.8 ± 3.04	< 0.0001
45 min after Pneumoperitoneum	85.10 ± 4.96	73.6 ± 4.18	< 0.0001
60 min after Pneumoperitoneum	82.7 ± 4.02	74.3 ± 5.10	< 0.0001
1 min after Release of pneumoperitoneum	83.07 ± 14.62	71.0 ± 5.42	< 0.0001
15 min after Release of pneumoperitoneum	84.87 ± 3.05	72.2 ± 5.56	0.0011
After extubation	86.87 ± 3.38	74.8 ± 4.97	< 0.0001

Table 4: Mean Post Operative Mean Blood Pressure in the two Groups (mmHg)

Time	Group Dex 0.25 Mean ± SD	Group Dex 0.5 Mean ± SD	Inter group p value
Post operative 1 hour	86.87 ± 3.38	75.4 ± 4.11	0.1323
Post operative 2 hour	87.7 ± 4.57	76.4 ± 5.27	0.7125
Post operative 3 hour	87.3 ± 3.12	77.2 ± 4.40	0.0546
Post operative 4 hour	86.9 ± 3.22	78.9 ± 6.34	< 0.0001
Post operative 5 hour	87.37 ± 5.87	77.6 ± 6.11	< 0.0001
Post operative 6 hour	87.90 ± 3.83	78.5 ± 3.23	< 0.0001
Post operative 12 hour	86.57 ± 4.26	78.1 ± 6.71	< 0.0001
Post operative 24 hour	92.97 ± 4.91	77.96 ± 4.9	< 0.0001

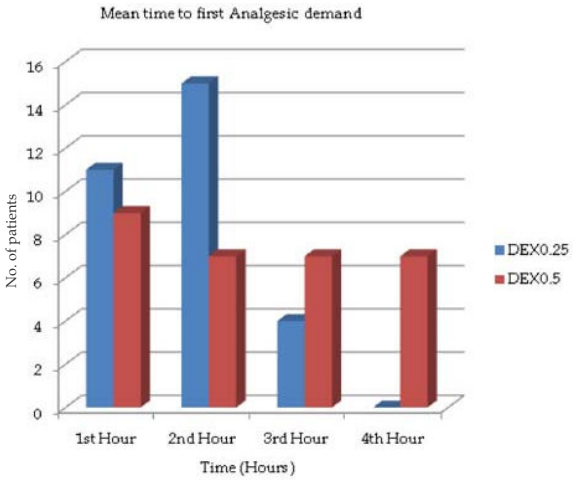

Fig. 1: Mean Post Operative Time to First Analgesic Demand in the two Groups

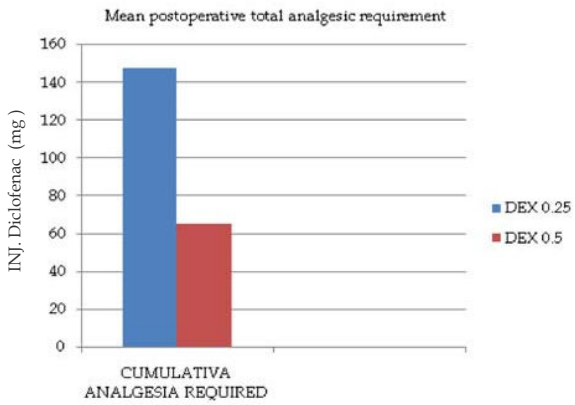

Fig. 2: Mean Post Operative Total Analgesic Consumption (Inj. Diclofenac) Mg

0.5–1.0 μg kg^{-1} were given intraoperatively whenever required to keep mean blood pressure within 20% of baseline value. In group Dex 0.25 total 25 patients (83.3%) required single top up, where as in DEX 0.5 group only 2 patients (6.7%) required single dose of fentanyl top up and the

difference being statistically significant.

Comparing the VAS between the two groups, the mean VAS was less in DEX 0.5 group than in DEX 0.25 group at all observed time points.

The time to first analgesic demand was later in the DEX 0.5 group as compared to the DEX 0.25 group (Fig. 1)

The mean total analgesic consumption of Diclofenac in Group Dex 0.25 was 147.50 ± 68.42 mg and in Group Dex 0.5 it was 65.0 ± 25.49 mg as depicted in figure 2.

Sedation scores were higher in group DEX 0.5 as compared to groups DEX 0.25 during the postoperative period.

Two patients in the DEX 0.5 group experienced dryness of mouth which was relieved by wetting of lips and oral mucosa with a sip of water.

Discussion

The hemodynamic alterations due to intense sympathetic stimulation accompanying laparoscopic surgery comprising of elevation in heart rate and rise in systolic, diastolic and mean arterial pressure are well known. Immediately after pneumoperitoneum, plasma level of norepinephrine, epinephrine and plasma renin activity is increased. Increased catecholamine level activates the renin-angiotensin-aldosterone-system (RAAS) leading to some characteristic hemodynamic alterations. The potential for life-threatening complications associated with such a response is also well documented.

Laparoscopic cholecystectomy is performed in reverse Trendelenberg position. This particular position causes diminished venous return which ultimately leads to further decrease in cardiac output. Patients with compromised cardiac function may not be able to tolerate the changes in afterload produced by pneumoperitoneum and it may have deleterious effects on their hemodynamics.

There is a strong relationship of both perioperative myocardial ischemia and postoperative myocardial infarction with anaesthetic and surgical events known to produce intense sympathetic stimulation, with or without hemodynamic abnormalities [5]. Thus, it is logical to look for methods to reduce sympathetic stimulation per se.

Various drugs and methods have been studied to prevent hemodynamic alterations due to stress of surgery and anaesthesia. Dexmedetomidine, a highly selective α2 agonist, has been used by many workers for attenuation of hemodynamic responses in various doses and along with various anaesthetic regimens for various types of surgeries. Dexmedetomidine infusion in the perioperative period in laparoscopic cholecystectomy provides better intraoperative and postoperative hemodynamic stability [6].

Keniya et al. showed that the increase in the heart rate during endotracheal intubation and laparoscopic insufflation was significantly attenuated in the dexmedetomidine group as compared to the control group. [6-11]. Mean heart rate was lower than in Group Dex 0.5 as compared to the group Dex 0.25 and significant differences were found at all-time points of the study period. Significant bradycardia was not noted in any of the cases in either group.

Bhatacharjee et al. noted that the MBP was significantly reduced during the intraoperative period and the reduction in MBP was significantly more in patients receiving dexmedetomidine than in patients receiving propofol. In the recovery room, MBP of both treatment groups was significantly lower than before surgery. MBP was significantly lower throughout the period of recovery in the Dexmedetomidine group as compared to the propofol group. They attributed it to the to additive sympatholytic effect of dexmedetomidine over hypotensive effect of propofol at the dosages used in their study. [6,11-15].

In both DEX 0.25 and DEX 0.5 baseline MBP fell to lowest mean after loading dose of dexmedetomidine. After that minimal change in MBP was observed in post intubation and after pneumoperitoneum, with the MBP being significantly lower in the DEX 0.5 group at all the study time intervals as compared to the DEX 0.25 group.

We observed in our study that none of the patients had any episode of bradycardia and hypotension in either of the dexmedetomidine groups which could be because we used lower maintenance dose without any loading dose. Studies using dexmedetomidine have commonly reported cardiovascular side effects such as bradycardia, sinus arrest and hypotension mainly because of sympatholytic effect. In several study reports, dexmedetomidine infusion rates ranging from 0.1 to 10 µg kg-1 hr-1 have been used. The studies with higher infusion rates had more incidences of adverse effects like hypotension and bradycardia [16].

Patients who received dexmedetomidine 0.5 infusion had lesser requirement of fentanyl and the hemodynamic parameters were much more stable than dexmedetomidine 0.25 infusion

group. Bajwa SS et al. in their study showed that dexmedetomidine decreased the dose of intraoperative opioids and isoflurane in achieving adequate analgesia and anaesthesia respectively [8,10,12,17,18,19].

Waleed M. et al. in their study found that, compared with placebo group, patients in the dexmedetomidine group had significantly lower visual analogue scale scores. [9,19-21].

The mean sedation score is more in DEX 0.5 group than in DEX 0.25 group at all observed time points (using modified ramsay sedation score) and patient satisfaction higher [12,21].

Dexmedetomidine lowers the cumulative analgesic consumption at all times during the post operative period and also delays time to first analgesic demand. Gourishankar Reddy Manne et al. in their study concluded that the rescue analgesia was required early (55.5 minutes.) in Group NS compared to dexmedetomidine groups (173 minutes in Dex 0.2 and 249 minutes in Dex 0.4 group) [11,14,21, 22].

Tufanogullari B et al., Turgut N et al., Massad M I et al. also demonstrated that patients receiving dexmedetomidine had lesser incidence of postoperative nausea and vomiting [14,15,23].

Conclusion

We conclude from our study that dexmedetomidine intravenous infusion in the dose range of 0.25 μg kg^{-1} hr^{-1} and 0.5 μg kg^{-1} hr^{-1} reduces the rise in heart rate and mean arterial pressure associated with the creation and maintenance of pneumoperitoneum during the laparoscopic surgical procedures. Thus, it provides perioperative hemodynamic stability in ASA I and II grade patients during laparoscopic surgeries because of their sedative, hypnotic, anxiolytic and sympatholytic properties [24]. Hence, dexmedetomidine infusion at 0.5 μg kg^{-1} hr^{-1} can be used as an anaesthetic adjuvant in laparoscopic surgeries to provide hemodynamic stability and facilitate smooth emergence from anaesthesia. It also affords added advantage of opioid sparing properties and in preventing post operative nausea and vomiting. However further study is required to evaluate its effect on hemodynamic parameters in high risk group patients with compromised cardio-respiratory function undergoing laparoscopic surgical procedures.

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