

Intramuscular Dexmedetomidine as Premedication for General Anaesthesia in Patients Undergoing Laparoscopic Cholecystectomy - A Comparative Study

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ABSTRACT

BACKGROUND

The efficacy of Intramuscular Dexmedetomidine, as premedication, in obtunding the hemodynamic responses during laryngoscopy, endotracheal intubation and pneumoperitoneum and also the perioperative and postoperative analgesic and anaesthetic requirement in patients undergoing laparoscopic cholecystectomy was studied.

METHODS

Study arm (Gr- D n=30) received Inj. Dexmedetomidine- 2 µg/Kg (1.5 ml. average) IM and control arm (Gr- R n=30) received Inj. Ranitidine HCL- 1.5 ml IM 1 hour before induction. Premedication with inj. Glycopyrrolate- 4 µg/Kg, Fentanyl Citrate 2.0 µg/Kg & inj. Ondansetron- 4 mg I V, induced with Inj. Propofol- 2 mg/Kg and intubated with Inj. Atracurium Besylate- 0.5 mg/Kg. Anaesthesia was maintained with N₂O, O₂ & Sevoflurane. Dose of Sevoflurane was increased if signs of light anaesthesia occurred, if signs persisted then repeat dose Fentanyl was given. Sevoflurane conc. was decreased if hypotension occurred and if persisted then phenylephrine was given. Bradycardia was treated with inj. Atropine 0.6 mg I.V. Patient was reversed with Inj. glycopyrrolate and neostigmine. Post-operative heart rate, NIBP, level of sedation, analgesic requirement was monitored for one hour. It is a prospective, double-blind, randomized, placebo-controlled clinical study.

RESULTS

Heart rate, mean arterial pressure, fentanyl requirement, sevoflurane requirement at different time intervals during operation and post operatively at 60 min. were analysed by pair t-test and was found to be statistically significant between two arms.

CONCLUSIONS

Inj. Dexmedetomidine (2 µg/Kg) as intramuscular premedication attenuates haemodynamic responses to laryngoscopy, endotracheal intubation & pneumoperitoneum & provides significant haemodynamic stability up to one hour postoperatively.

KEY WORDS

Dexmedetomidine, Intubation, Laparoscopic Surgery, Laryngoscopy, Pneumoperitoneum

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BACKGROUND

The challenge in anaesthesia is to maintain a balance between the stress of the laryngoscopy, intubation and surgery with the cardio-respiratory depressant effects of deeper levels of anaesthesia. Laryngoscopy and intubation is a strong stimulus for cardiovascular system.^[1] Response is greater with increasing force and duration of laryngoscopy.^[2] The elevation in arterial pressure typically starts within 5 seconds of laryngoscopy, peaks in 1 to 2 minutes and returns to control level within 5 minutes.^[1] It can be prevented by increasing the depth of anaesthesia. Volatile anaesthetic agents, aerosol or application of topical anaesthetics may be beneficial. ^[3] Large doses of fentanyl (5-10 µg/Kg) may attenuate the response but causes prolonged respiratory depression. Topical anaesthetics, parenteral opioids and beta blockers may be used in combination with narcotics.

Dexmedetomidine, a selective and specific α_2 -adrenergic agonist is beneficial for premedication to reduce sympathetic activity with attenuation of neuroendocrine and haemodynamic responses to surgery and anaesthesia and to decrease anaesthetic and analgesic requirement. Laparoscopic surgeries have multiple benefits compared to open procedures, but it presents several challenges for the anaesthesiologist. ^[4] The pneumoperitoneum and the patient position required for laparoscopy induces pathophysiologic changes that complicate anaesthetic management. Several drugs and interventions have been tried to reduce complications e.g. use of remifentanyl, clonidine, or gasless laparoscopy.^{[5],[6],[7]} In view of these observations the present study was designed to evaluate the efficacy of intramuscular Dexmedetomidine as premedication for blunting the hemodynamic response to laryngoscopy, endotracheal intubation and pneumoperitoneum and dose requirement of intra-operative analgesic and anaesthetic agents in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

METHODS

The present study was carried out from February 2016 to January 2017 after approval from the Institutional Ethics Committee. Informed consent was obtained from all patients included in the study. 60 (n=60) patients aged 18-50 years of ASA-grade 1 and 2 undergoing Laparoscopic Cholecystectomy under General anaesthesia were included in the study. They were divided into two groups-

1. Group D (n=30) received Inj. Dexmedetomidine- 2 µg/Kg (total volume 1.5 ml average) I.M.
2. Group R (n=30) received Ranitidine HCL- 1.5 I.M. as placebo.

Exclusion criteria were patient refusal, known hypersensitivity to the drugs, hypertensives on two drug regime, mental retardation or psychiatric illness and pregnancy.

The patients were brought to the observation room and baseline parameters such as heart rate (HR), blood pressure (systolic (SBP), diastolic (DBP) and mean arterial (MAP)) and oxygen saturation (SpO₂) were measured. They were then

randomly divided into 2 groups with every second patient in the study group.

Patients received Dexmedetomidine or Ranitidine IM 60 minutes before induction of general anaesthesia. The baseline heart rate, blood pressure (systolic, diastolic and mean), oxygen saturation and ECG were monitored.

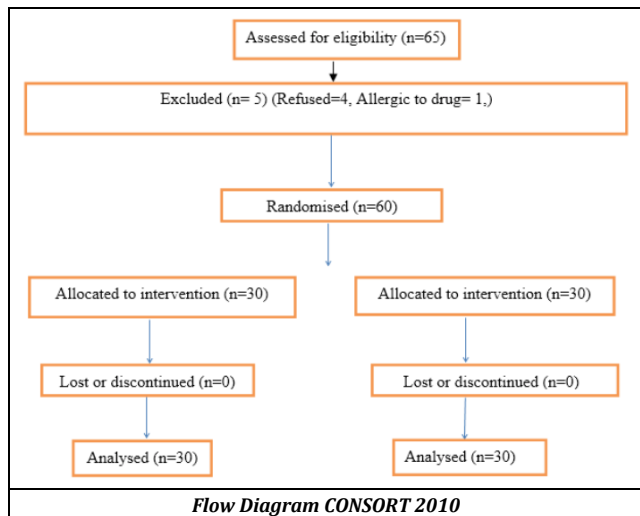
The level of sedation was assessed by Ramsay Sedation Score (RSS).^[8] In both groups before induction, baseline heart rate, blood pressure (systolic, diastolic and mean), oxygen saturation and ECG were recorded. I.V. infusion was started with Ringer's lactate at a rate of 6-8 ml/Kg/hr. Pre oxygenation with 100% O₂ was started and premedication was given with inj. Glycopyrrolate- 4 µg/Kg, inj. Ondansetron- 4 mg I.V., inj. fentanyl citrate 2.0 µg/Kg I.V. and Inj. Midazolam-0.05 mg/Kg I.V. Patients were induced with Inj. Propofol 2 mg/Kg and intubated with Inj. Atracurium besylate- 0.5 mg/Kg. Anaesthesia was maintained with 70% N₂O in O₂ and Sevoflurane inhalation. Neuromuscular block was maintained with inj. Atracurium besylate 0.15 mg/Kg. Inj. Paracetamol 1 gm was given intraoperatively. Laparoscopy was performed with the table at a 15° head-up tilt and intra-abdominal pressure (IAP) was maintained at 10-12 mmHg.

Sevoflurane was administered using the lowest possible end-tidal concentration according to the following scheme: If hypertension (MAP 20% or more over the baseline values or over 110 mmHg), tachycardia (HR 20% or more over the baseline values or over 100 bpm), or signs of light anaesthesia (sweating, lacrimation, flushing) occurred, administration of Sevoflurane 0.6% end-tidal concentration was begun. If MAP and/or HR did not decrease to the predetermined level within 4 mins, the end-tidal concentration of Sevoflurane was increased with 0.2% steps every 4 min if necessary up to a maximum of 2.0%. If the end-tidal Sevoflurane concentration of 2.0% was not sufficient, inj. Fentanyl was given in 1.0 µg/Kg increments. When BP and HR decreased and were within the predetermined limits, the Sevoflurane concentration was decreased every 4 mins. in 0.2% steps as long as the values remained within the accepted limits. End-tidal Sevoflurane concentration was measured using an anaesthetic agent monitor. The overall mean end-tidal concentration of Sevoflurane during laparoscopy was assessed. If hypotension (MAP 20% or more below the baseline value or below 70 mmHg) occurred, Sevoflurane concentration was first reduced with 0.2% steps every 4 min. If MAP remained below the predetermined limits even after discontinuation of Sevoflurane, ringer's lactate solution 250 mL was given over a 5-min period, if hypotension persisted it was treated with inj. Phenylephrine 50 µg I.V. bolus dose.

Bradycardia, i.e. HR less than 50 per minute lasting more than 1 min, was treated with inj. atropine 0.6 mg I.V.

Sevoflurane was discontinued at the start of laparoscopy port closure. After completion of surgery neuromuscular block was reversed with Inj. glycopyrrolate 0.01 mg/Kg and Inj. neostigmine 0.05 mg/Kg and patient was extubated when adequate spontaneous ventilation was established. All the patients were shifted to PACU for post-surgical recording of parameters (heart rate and NIBP at 30 mins. and 60 mins. after recovery, level of sedation at 60 mins, analgesic requirement and side effects if any noted up to 60 mins). In PACU all patients received moist O₂ inhalation for 2 hours.

Rescue analgesic was administered on patients demand or when the VAS score ≥ 4 whichever earlier, in the form of inj. Tramadol 3 mg/Kg I.V. over 30 mins. diluted in 50 ml NS. The time of first rescue analgesic was noted.



Statistical Analysis

Data have been summarized by Descriptive Statistics. Numerical variables have been compared between groups by unpaired t-test. Categorical variables have been compared between groups by Chi square test. All analyses were 2-tailed and $p < 0.05$ was considered statistically significant. The primary variable of our study was to detect a 10-15% difference in hemodynamic parameters between the groups with 80% statistical power and a significance level(α) of 0.05 (two-tailed) and we calculated a sample size of 60 patients by using the software Statistica Version 6 (Tulsa, Oklahoma: StatSoft Inc.,2001).

RESULTS

The demographic parameters were comparable among the two groups. The 2-tailed unpaired t-test was applied. The difference of mean heart rate before induction and after 1 min and 5 mins following laryngoscopy and intubation was statistically highly significant in the two groups ($p = 0.000$, $p = 0.000$, $p = 0.000$ respectively). The difference persisted after pneumoperitoneum, after change of patient position and 15 mins after pneumoperitoneum; 30 mins., after pneumoperitoneum the difference was not significant ($p = 0.154$) and 5 mins. After release of pneumoperitoneum difference was significant (Table 1). Statistically significant difference ($p < 0.05$) was found at 30 mins. And 60 mins., of post-operative period and the mean HR was lower in Group D (table 1).

Applying the 2-tailed unpaired t-test (assuming equal variances) between the mean of MAP of each group $p < 0.05$ was found at before induction, during 1 min and 5 mins following laryngoscopy and intubation, after pneumoperitoneum, after change of patient position, 15 mins., and 30 mins., after pneumoperitoneum and 5 mins., after release of pneumoperitoneum and $p > 0.05$ was found before premedication. Hence baseline MAP was comparable

among the groups and statistically significant difference is found at most of the time in mean MAP between the two groups before induction, during laryngoscopy and intubation, during pneumoperitoneum and even after release of pneumoperitoneum. (table 2). Statistically significant difference was found at 30 mins Group R- 93.0 ± 6.731 and Group D- 84.5 ± 4.883 and at 60 mins. Group R- 95.7 ± 6.747 and Group D- 86.6 ± 3.838 of post-operative period and the mean MAP is significantly lower in Group D (table 2).

The total Fentanyl requirement ($\mu\text{g}/\text{Kg}$) and the mean end-tidal Sevoflurane requirement during surgery among the groups are statistically significant. There is reduction in Fentanyl requirement in Group D. Group P: Group D 3.63 ± 0.718 ; 2.83 ± 0.592 (table 3) and also reduction in end-tidal Sevoflurane requirement in Group D. (table 3).

Variables	Group R (n= 30) (mean \pm SD)	Group D (n=30) (mean \pm SD)	Statistical Test Result Unpaired t-Test	Significance
Baseline/Before pre-medication	81.3 \pm 8.188	80.3 \pm 6.450	$p = 0.601$	Not significant
Before induction	93.5 \pm 4.754	62.3 \pm 9.411	$p = 0.000$	significant
1 minute after laryngoscopy & intubation	110.8 \pm 5.222	80.6 \pm 5.899	$p = 0.000$	significant
5 minutes after laryngoscopy & intubation	89.3 \pm 6.369	68.0 \pm 7.502	$p = 0.000$	significant
After pneumoperitoneum	87.5 \pm 5.685	77.1 \pm 7.508	$p = 0.000$	significant
After change of position	89.1 \pm 3.652	78.0 \pm 11.371	$p = 0.000$	significant
15 minutes after pneumoperitoneum	87.0 \pm 5.003	76.1 \pm 20.481	$p = 0.006$	significant
30 minutes after pneumoperitoneum	80.6 \pm 6.688	75.8 \pm 16.914	$p = 0.154$	Not significant
5 minutes after pneumo release	82.3 \pm 6.188	75.5 \pm 4.462	$p = 0.000$	significant
30 min post op	85.1 \pm 8.755	67.2 \pm 9.331	$p = 0.000$	highly significant
60 min post op	88.4 \pm 9.489	71.4 \pm 2.372	$p = 0.000$	

Table 1. Comparing Heart Rate (in Beats/Minute) among the Study Groups at Specified Points of Time During Surgery (N= 60) Original

Variables	Group R (n= 30) (mean \pm SD)	Group D (n=30) (mean \pm SD)	Statistical Test Result Unpaired t-Test	Significance
Baseline/ Before pre-medication	90.5 \pm 6.174	88.4 \pm 5.028	$p = 0.154$	Not significant
Before induction	89.5 \pm 5.131	74.6 \pm 4.461	$p = 0.000$	significant
1 minute after laryngoscopy & intubation	111.8 \pm 5.222	94.1 \pm 4.604	$p = 0.000$	significant
5 minutes after laryngoscopy & intubation	91.4 \pm 5.969	78.9 \pm 3.418	$p = 0.000$	significant
After pneumoperitoneum	97.6 \pm 5.424	91.3 \pm 5.609	$p = 0.000$	significant
After change of position	98.2 \pm 5.020	90.3 \pm 7.530	$p = 0.000$	significant
15 minutes after pneumoperitoneum	102.7 \pm 5.266	92.4 \pm 6.306	$p = 0.000$	significant
30 minutes after pneumoperitoneum	103.7 \pm 5.344	91.8 \pm 6.283	$p = 0.000$	significant
5 minutes after release of pneumo.	92.3 \pm 6.929	84.1 \pm 3.652	$p = 0.000$	significant
30 minutes postoperative	93.0 \pm 6.731	84.5 \pm 4.883	$p = 0.000$	highly significant
60 minutes postoperative	95.7 \pm 6.747	86.6 \pm 3.838	$p = 0.000$	highly significant

Table 2. Comparing Mean Arterial Pressures (mmHg) among the Study Groups at Specified Time Periods during Surgery and Postop. (N=60) Original

Variable	Group R (n=30) (mean ± SD)	Group D (n=30) (mean ± SD)	Statistical Test Result	Statistical Significance
Total fentanyl requirement	3.63 ±0.718	2.83±0.592	Unpaired t-test p=0.000	Highly significant
Mean end-tidal isoflurane requirement	0.440±0.675	0.240±0.675	Unpaired t-test p=0.000	Highly significant

Table 3. Comparing Total Fentanyl (µg/Kg) and Mean End-Tidal Sevoflurane (Concentration in %) Requirement During Surgery among the Study Groups (N=60) Original

	Group R	Group D	Statistical Test Result	
Bradycardia	0 (0%)	8 (26%)	Chi square test p= 0.00	highly significant
Level of Sedation				
Score 1	21(70%)	0	Chi square test p= 0.00(For all 3 readings)	highly significant
Score 2	9(30%)	25(83.3%)		
Score 3	0	5(16.7%)		

Table 4. Comparing Adverse Effects During Surgery among the Groups (N=60), Bradycardia and Sedation-Original

Variable	Group R n= 30	Group D n= 30	Statistical Test Result	Significance
Rescue analgesic needed	24(80%)	8(26.7%)	Chi square test p=0.000	highly significant
No analgesic needed	6(20%)	22(73.3%)		

Table 5. Comparing Need for Rescue Analgesic among the Study Groups up to 60 Minutes Post-Operative Period (N=60) Original

Incidence of adverse effect (bradycardia) during surgery is more in Group D on Chi square test. (p value= 0.000) is highly significant (table 4). The level of sedation at 60 mins of post-operative period was evaluated according to Ramsay Sedation Score and the patients of Group D were found to be more sedated. The incidence of adverse effects (bradycardia) up to 60 mins., of post-operative period between the groups was significant and the incidence was more in Group D 5(16.6%) and 0 (0%) for Group P, so Chi square test. (p value= 0.000).

Statistically significant difference in need for rescue analgesic upto 60 mins., of post-operative period between the groups was noted and the patients in Group D required less rescue analgesic. Table-5.

DISCUSSION

Our study showed that inj. Dexmedetomidine 2µg/Kg I.M. as premedication 60 minutes before induction blunted the hemodynamic response to laryngoscopy and endotracheal intubation compared to placebo. It also attenuated the haemodynamic changes during peritoneum insufflation in laparoscopic surgery.

Sulaiman S et al, Aksu R et al, Ghodki PS et al, in different studies also observed that Inj. Dexmedetomidine, as premedication attenuated cardiovascular responses to laryngoscopy and tracheal intubation.^[9,10,11] D. P. Bhattacharjee et al observed that in patients undergoing elective laparoscopic cholecystectomy with Dexmedetomidine intravenous infusion the mean arterial pressure and heart rate were significantly less after intubation and pneumoperitoneum.^[12]

Heart rate increased in Group R after pneumoperitoneum, after change of patient position till 15 mins after pneumoperitoneum, it reduced to near baseline at 30 mins of

pneumoperitoneum and 5 mins after release of pneumoperitoneum. In Group D the heart rate did not change much from the baseline values at any stage.

Mean arterial pressure (MAP) increased in Group R after pneumoperitoneum and increased further at 15 mins and 30 mins of pneumoperitoneum. The MAP decreased after 5 mins of release of pneumoperitoneum and reached near the baseline values. In Group D the MAP increased slightly after pneumoperitoneum did not change much at 15 mins and 30 mins of pneumoperitoneum and all the values were close to the baseline values. The MAP decreased 5 mins after release of pneumoperitoneum and the mean value was just below the baseline values. The MAP values between the groups have highly significant statistical difference at all stages of pneumoperitoneum including 5 mins after release of pneumoperitoneum (p= 0.000), Ghodki PS et al, found that during laparoscopy MAP and heart rate increase was low in patients receiving dexmedetomidine. Our study results corroborate with this study.^[11]

In our study, the mean inj. Fentanyl requirement in Group R were 3.63 µg/Kg and for Group D were 2.83 µg/Kg respectively. Difference is statistically highly significant between the groups (p= 0.000). Scheinin H et al, also found that pretreatment with a single I.M. injection of 2.5 microgram/Kg Dexmedetomidine is efficient in decreasing the intraoperative fentanyl requirement.^[13]

The overall mean end-tidal sevoflurane concentration required during surgery to maintain the pre-defined anaesthesia endpoints in Group R was 0.44% and in Group D it was 0.24% and on statistical analysis there is highly significant difference between the groups.

V. M. Keniya et al (2011) and Bajwa et al studied sixty patients scheduled for elective surgery who received isoflurane-opioid-dexmedetomidine anaesthesia and found that the need for thiopentone, fentanyl and isoflurane was decreased. ^[14,15] Ghodki PS et al observed that dexmedetomidine as an anaesthetic adjuvant in laparoscopic surgery decreased mean Isoflurane concentration requirement during surgery. ^[11]

The mean post-operative heart rate in Group R at 30 mins and 60 mins following reversal were 85.1 per min. and 88.4 per min respectively which was higher than baseline values of heart rate in Group D at 30 mins and 60 mins following reversal were 67.2 per min. and 71.4 per min. respectively which was lower than baseline values.

The mean post-operative mean arterial pressure (MAP) in Group R at 30 and 60 mins following reversal were 93.0 mmHg and 95.7 mmHg respectively which was higher than baseline values and MAP in Group D at 30 mins and 60 mins were 84.5 mmHg and 86.6 mmHg respectively was lower than baseline values. 80% of the patients in Group P and 26.7% patients in Group D, in our study required rescue analgesic within 1 hour following recovery in PACU which was statistically significant (p=0.000).

When assessed for post-operative level of sedation using Ramsay Sedation Score (RSS) at 60 mins after recovery at post anaesthesia care unit it was found that 70% patients were anxious or restless (RSS grade 1) and 30% patients were co-operative and calm (RSS grade 2) in Group R and in Group D 83% of the patients were calm and co-operative

(RSS grade 2) and 17% patients responded to commands only (RSS grade 3). ($p=0.000$) between the groups on statistical analysis. SR Prasad et al observed that Dexmedetomidine facilitates adequate sedation for mechanical ventilation and also early extubation as compared with Fentanyl. [16,17]

In Group D 8 patients (26.7%) developed bradycardia during surgery and 5 patients (16%) in post anaesthesia care unit all of them responded promptly to inj. Atropine 0.6 mg I.V. This was found to be statistically significant on analysis ($p=0.000$). No patients in Group R developed any other adverse effect requiring intervention. No other adverse effect was observed in Group D. No patients in Group R developed bradycardia or any other adverse effect.

CONCLUSIONS

Inj. Dexmedetomidine (2 µg/Kg) as intramuscular premedication attenuates haemodynamic responses to laryngoscopy, endotracheal intubation & pneumoperitoneum compared to placebo & also provides significant haemodynamic stability up to 60 minutes of post-operative period. It also significantly reduces per-operative analgesic and anaesthetic requirement when used as premedication. Significant bradycardia during surgery & also during post-operative period is sometimes a needed intervention but there was significant post-operative sedation and decreased analgesic requirement up to 60 minutes.

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