

DEXMETETOMIDINE AS A SINGLE BOLUS DOSE IN LAPAROSCOPIC CHOLECYSTECTOMY UNDER GENERAL ANESTHESIA – A COMPARISON OF DIFFERENT DOSES

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ABSTRACT

Introduction

Dexmedetomidine has an ideal pharmacodynamic profile for attenuation of stress response during general anesthesia for laparoscopic cholecystectomy. Since, the value of dexmedetomidine as a single premedication dose remains largely unexplored, this study compared dexmedetomidine in 0.5µg/kg and 1µg/kg dose for laparoscopic cholecystectomy under general anesthesia.

Objectives

The primary objective of this study was to compare dexmedetomidine in a single premedication dose of 0.5µg/kg and 1µg/kg in terms of hemodynamic (heart rate and mean arterial pressure) changes to critical incidences such as laryngoscopy, endotracheal intubation, pneumoperitoneum and extubation. The secondary objectives were to compare induction dose of propofol required, sedation scores in the immediate post anesthesia period and adverse events such as bradycardia and hypotension.

Methodology

This was a prospective double blind study. Ninety-two patients aged 18-55 years of either gender of American Society of Anesthesiologists physical status I-II were randomly allocated into two groups to receive either Dexmedetomidine 1µg/kg or 0.5µg/kg slowly IV over 10 minutes as a premedication before induction. Heart rate, Mean arterial pressure, induction dose of propofol, sedation scores, and adverse events were compared.

Results

The patient characteristics, Fentanyl consumption, duration of surgery and anesthesia in both groups were comparable. There was comparable attenuation of hemodynamics in both groups during laryngoscopy and intubation. Dexmedetomidine in 1µg/kg compared to 0.5µg/kg had significantly better attenuation of hemodynamics from 1 minute to 40 minutes of pneumoperitoneum. After 40 minutes, there was no attenuation in either group. The post anesthesia sedation scores were comparable. The induction dose of propofol was significantly less and the incidence of bradycardia was significantly higher with dexmedetomidine 1µg/kg.

Conclusion

This study demonstrates that a premedication dose of Dexmedetomidine in 1µg/kg compared to 0.5µg/kg has significantly better attenuation of hemodynamics from 1 minute to 40 minutes of pneumoperitoneum.

KEYWORDS

Dexmedetomidine, laparoscopic surgery, heart rate, mean arterial pressure



INTRODUCTION

Dexmedetomidine is ideal as an adjuvant to general anesthesia for different procedures including laparoscopic cholecystectomy. Dexmedetomidine attenuates the sympathetic activity, has drug sparing effects and provides sedation without respiratory depression making it favorable for anesthesia for laparoscopic surgeries.¹

Though the procedure of laparoscopic approach for cholecystectomy has proven superiority over an open procedure in terms of less postoperative pain, small incisions, shorter hospitalization and faster functional recovery, the surgical stress response is equal or probably increased.² Pneumoperitoneum combined with the positional changes (reverse Trendelenburg position) results in significant hemodynamic and respiratory changes. Carbon dioxide used to create pneumoperitoneum can lead to hypercapnia. Both hypercapnia and pneumoperitoneum stimulate the sympathetic nervous system, which causes release of catecholamine and vasopressin and also activation of the renin-angiotensin system.³ In addition, the anesthetic interventions like laryngoscopy, tracheal intubation and extubation evoke hemodynamic stress response leading to hypertension and tachycardia. Studies have consistently observed promising results with significant implications whenever dexmedetomidine was employed as an adjuvant to general anesthesia for this purpose.

Since, the value of dexmedetomidine as a single premedication dose for the duration of anesthesia for laparoscopic cholecystectomy remains largely unexplored, this study aimed to compare two different doses of dexmedetomidine as a single premedication dose for patients undergoing laparoscopic cholecystectomy under general anesthesia in terms of hemodynamic response to critical incidences such as laryngoscopy, endotracheal intubation, pneumoperitoneum and extubation as well as induction dose of propofol and sedation scores in the postoperative period in patients undergoing laparoscopic cholecystectomy.

METHODOLOGY

This prospective double-blind study was conducted after ethical approval from the institutional review committee of Nobel medical college teaching hospital (IRC-116/2018). American Society of Anesthesiologists physical status I-II adults aged 18-55 years of either gender undergoing elective laparoscopic cholecystectomy under general anesthesia were enrolled in the study. A written informed consent for the study was obtained from all patients. Exclusion criteria included patient refusal, known hypersensitivity to the study drugs, anticipated difficult airway (Mallampatti Grade III-IV), obesity (BMI >25), cardiac disorders, hypertension, patients on digoxin or beta-blockers, baseline heart rate (HR) less than 60 beats per minute and, pregnant and lactating patients. Patients with intubation attempt lasting longer than 15 seconds, multiple intubation attempts (two or more) and surgeries lasting for more than 60 minutes were not considered in the study.

After a thorough preoperative evaluation, standard premedication with Alprazolam 0.5 mg per oral was administered to the patients a day before surgery. The patients were kept nil per oral for six hours before anesthesia. In the operating room, standard monitors were attached. Baseline HR, systolic, diastolic, and mean arterial pressures (MAP) and oxygen saturation were recorded. The patients were then randomly allocated into two groups A and B by lottery method. Both the investigator and the patient were unaware of the group allocation. The study drug was loaded and delivered by a third person not involved in the study. Patients belonging to group A were given Dexmedetomidine 0.5µg/kg diluted with 0.9% saline to make 12.5ml volume, slowly IV over 10 minutes using syringe pump. Patients belonging to group B were given Dexmedetomidine 1µg/kg slowly IV over 10 minutes using syringe pump. It was diluted with 0.9% saline to make 25ml volume and a concentration not more than 4µg/ml. This was followed in each group by fentanyl 2µg/kg and Propofol 1% injection in incremental dose until loss of eyelash reflex was attained. The induction dose of Propofol was recorded. Isoflurane at 0.5% was turned on and vecuronium 0.1mg/kg was given. One minute after vecuronium injection, Isoflurane was increased to 2% to deepen the anesthesia. Three minutes after Vecuronium (expected onset of paralysis), direct laryngoscopy and intubation was commenced. HR and MAP were recorded before giving the test drug, after administration of test drug at 2 minutes and 5 minutes, after induction, after intubation at 1 minute, 5 minutes and 10 minutes. The maintenance of anesthesia was done by Isoflurane, Oxygen and Vecuronium with intermittent positive pressure ventilation along with Fentanyl titrated as needed. Isoflurane was used in the lowest possible concentration necessary to keep blood pressure and heart rate within 20% limits of the baseline values. The inspiratory concentration of Isoflurane was adjusted in steps of 0.2% when needed to keep the hemodynamic parameters acceptable. Fentanyl in increments of 0.4µg/kg was given when inspiratory isoflurane concentration exceeded 1%. In both groups, additional adjuvant was provided in the form of Diclofenac or Propofol IV after Fentanyl exceeded 2µg/kg. Hemodynamics at the time of peritoneal insufflation was noted at 1 minute, 10 minutes thereafter every 10 minutes till 60 minutes. The cases where the duration of surgery was more than 60 minutes were excluded from the study.

Intra-abdominal pressure was maintained at 12-14mmHg throughout the laparoscopic procedure. The patients were mechanically ventilated to keep the ET_{CO}₂ between 35-40mmHg. At the end of surgery, residual effect of neuromuscular blockade was reversed by Neostigmine 2.5mg and Glycopyrrolate 0.4mg. Patients were then extubated and transferred to the recovery ward. The post extubation HR and MAP were recorded at 2 minutes and 5 minutes. The duration of surgery and anesthesia and total Fentanyl consumption during surgery were recorded. Sedation scores were recorded after extubation using modified Ramsay sedation scoring at 15, 30, 45 and 60 minutes and adverse effects like bradycardia, hypotension if any were recorded.



Clinically relevant hypotension was defined as decrease in mean arterial pressure by 20% or more from baseline value. It was initially treated with 200ml of ringer's lactate solution. If this was ineffective, IV Mephenteramine 5 mg would be given. Clinically relevant bradycardia was defined as a heart rate decrease to less than 45 beats per minute or bradycardia along with hypotension. This was treated with IV Atropine 0.01mg/kg.

Statistical analysis

Numeric data has been expressed as mean±SD. Chi square test was applied for non-parametric data. Paired t-test was used for parametric data within group and Independent t-test was applied for parametric data between the groups. A p-value <0.05 was considered statistically significant. The software SPSS version 21 was used for analysis.

RESULT

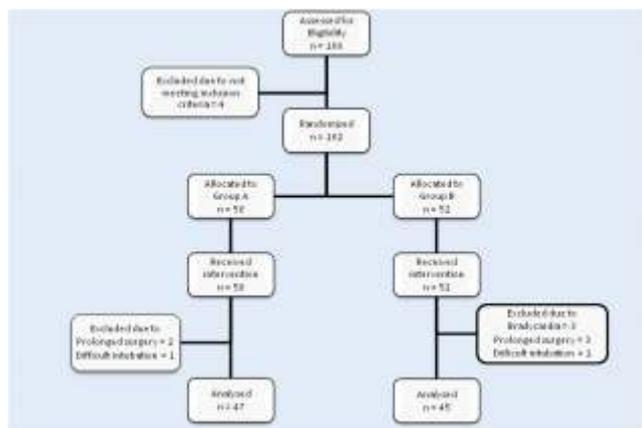


Figure 1: CONSORT flow chart

A total of 102 patients were randomized and 92 patients were enrolled for the study (Figure 1). The patient characteristics (Table 1), total Fentanyl consumption, duration of surgery and anesthesia in both groups were comparable but the induction dose of Propofol till loss of eyelash reflex in group B was significantly less (Table 2).

The HR and MAP at baseline were comparable in both the groups. There was a significant decrease in both HR and MAP compared to the respective baseline in both groups till 1 minute after pneumoperitoneum. Thereafter, the changes in HR and MAP were comparable in either group, except for 1 minute after extubation where significant increase was noted compared to baseline. When comparing both groups, there was a significant difference in both HR and MAP from 1 minute to 40 minutes of pneumoperitoneum (p-value < 0.05). HR and MAP at all other readings were comparable. (Figure 2, 3)

Table 1 – Patient characteristics

Parameters	Group A (mean ± SD)	Group B (mean ± SD)	P – value	
Age (yr)	40.19 ± 9.26	40.29 ± 10.70	0.963	
Weight (kg)	61.32 ± 14.33	64.09 ± 11.47	0.31	
Gender	Female	34 (72.34)	26 (57.78)	0.19
	Male	13 (27.66)	19 (42.22)	
ASA	I	42 (89.36)	40 (88.89)	1
	II	5 (10.64)	5 (11.11)	

Table 2 – Propofol, Fentanyl, duration of surgery and anesthesia

Parameters	Group A (mean ± SD)	Group B (mean ± SD)	P – value
Propofol (mg)	67.69 ± 14.17	59.78 ± 16.99	0.018
Fentanyl (µg)	112 ± 18.96	104.22 ± 24.45	0.064
Duration of Surgery (min)	53.38 ± 12.61	55.69 ± 10.77	0.349
Duration of Anesthesia (min)	64.11 ± 13.36	68.22 ± 9.45	0.093

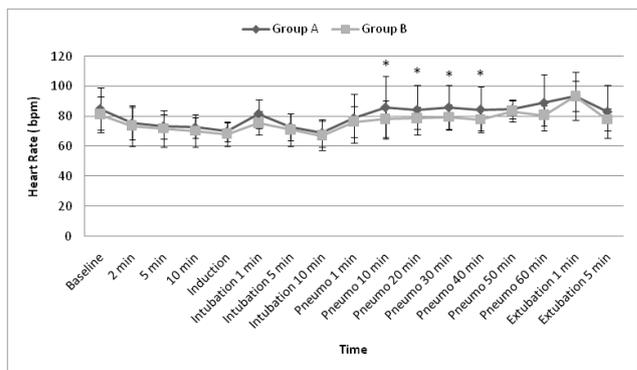


Figure 2: Heart Rate changes between the groups, * = P<0.05 between groups

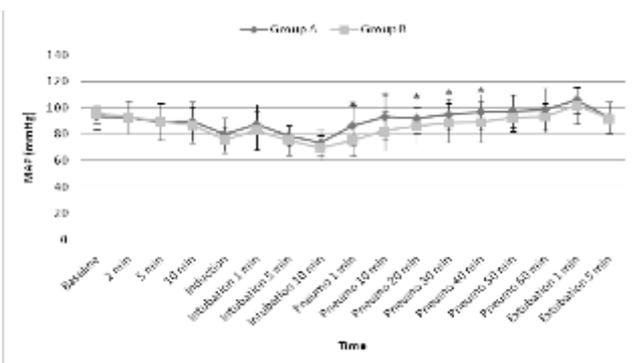


Figure 3 - MAP changes between the groups, * = P<0.05 between groups

Table 3 - Ramsay Sedation Score

Median sedation scores	Group A		Group B		P-value
	Median	Range	Median	Range	
RSS 15 min	2	2-4	2	2-4	0.161
RSS 30 min	1	1-3	1	1-3	0.517
RSS 45 min	1	1-2	1	1-2	0.641
RSS 60 min	1	1-1	1	1-1	-



The median RSS 15 minutes after extubation till 60 minutes in both groups were comparable.

Adverse events

Adverse events such as hypotension and bradycardia were seen in both groups. But, significantly high incidence of bradycardia was observed with dexmedetomidine 1µg/kg (P=0.048). Out of these, three patients receiving dexmedetomidine 1µg/kg had to be treated with atropine and were subsequently excluded from the study.

Table 4 - Adverse events

Adverse events	Group A n (%)	Group B n (%)	OR (95%CI)	P value (Fisher test)
Hypotension	1 (2.1)	4 (8.9)	0.223	0.198
Bradycardia	2 (4.3)	8 (17.8)	0.206	0.048

DISCUSSION

Dexmedetomidine has an ideal pharmacodynamic profile for attenuation of stress response during laryngoscopy, tracheal intubation, CO₂ pneumoperitoneum or extubation. The role of a loading as well as a maintenance dose of dexmedetomidine has been regularly studied. But the effect of a single premedication dose of dexmedetomidine in the whole period of laparoscopic cholecystectomy is little known about. So, we compared dexmedetomidine in a premedication dose of 0.5µg/kg to a 1µg/kg for laparoscopic cholecystectomy.

Laryngoscopy and tracheal intubation

In our study, either dose was associated with comparable attenuation of hemodynamics. Studies similar to ours comparing Dexmedetomidine 0.5µg/kg with 1µg/kg using Fentanyl 2µg/kg during induction have similar result to ours.^{4,5} But in another study, when Fentanyl in 1µg/kg dose at the induction of anesthesia a 0.5µg/kg dose was not able to attenuate the hemodynamics.⁶ So, it is likely that effectiveness of dexmedetomidine in 0.5µg/kg dose was associated with use of Fentanyl 2µg/kg at induction.

Pneumoperitoneum

Our finding suggests dexmedetomidine in 1µg/kg compared to 0.5µg/kg dose was significantly better at controlling both HR and MAP for the first 40 minutes. One study found comparable hemodynamics during the pneumoperitoneum of 80 minutes between a 0.5µg/kg and 1µg/kg dose of dexmedetomidine when N₂O was used during maintenance of anesthesia.⁷ Contrary to this, another study used Fentanyl 2µg/kg and N₂O for the maintenance of anesthesia and found dexmedetomidine 1µg/kg had significantly better hemodynamics throughout the pneumoperitoneum of 90 minutes when compared to a dose of 0.7µg/kg.⁸ The use of N₂O could be associated with the attenuation of hemodynamics although pharmacologic interaction between Dexmedetomidine and N₂O in attenuating hemodynamics is not yet established. Our study found neither dose of dexmedetomidine was sufficient to control the hemodynamics beyond 40 minutes

of pneumoperitoneum, suggesting a maintenance dose might be needed to effectively blunt the hemodynamic stress response. Khare et al observed dexmedetomidine when used as a loading dose of 1µg/kg followed by maintenance of 0.6µg/kg/hr provided stable intraoperative hemodynamics during laparoscopic cholecystectomy.⁹

Extubation

In our study, compared from the baseline and the immediate pre extubation values, the post extubation values in either group were significantly increased, so neither dose was effective in attenuating the hemodynamics at extubation. In a study, dexmedetomidine as a premedication in both 0.5µg/kg and 1µg/kg dose significantly attenuated the hemodynamic parameters at the time of extubation after 80 minutes of surgery.⁴ The maintenance of anesthesia was done using N₂O and Sevoflurane till the end of surgery. In another study, single premedication dose of dexmedetomidine in 1µg/kg and 2µg/kg had highly significant attenuation of HR and MAP after extubation at 1 minute and 5 minutes, though the duration of anesthesia in this study was just 30 minutes.¹⁰

Propofol induction dose

In our study, a significantly less dose of propofol was required with dexmedetomidine 1µg/kg. The mean reduction in induction dose of propofol required with dexmedetomidine 0.5µg/kg was 45% whereas with dexmedetomidine 1µg/kg was 53.5%, compared to a standard propofol dose of 2 mg/kg. Khare et al observed 36% and Sen et al observed 48.08% reductions in the induction dose of Propofol when Dexmedetomidine 1µg/kg was compared to a placebo using bispectral index.^{9,11} Similarly, a 62.5% reduction was observed by Godki et al using entropy.¹² The pharmacologic interaction of Dexmedetomidine with Propofol has been the suggested mechanism for the decrease in Propofol requirement.

Sedation scores

There was minimal residual sedation in both groups in post-anesthesia period which can be explained by limited effectiveness observed for the premedication dose beyond 40 minutes of pneumoperitoneum.

Adverse events

In the present study, 15 patients developed adverse events. Across the groups, three patients developed hypotension that was managed with bolus of 200ml Ringers lactate solution. A total of 12 patients developed bradycardia with significant difference in between groups. Two patients had severe bradycardia after induction and one patient developed bradycardia with hypotension. Hence, immediate atropine was administered in these three patients.

The usage of Dexmedetomidine in a higher dose (1µg/kg) has been attributed to higher incidence of adverse events such as bradycardia and hypotension due to its sympatholytic properties.¹³ A higher serum concentration attained secondary to either higher dose of drug or higher concentration of the infusion (>4µg/ml) have been observed



as contributory factors for occurrence of bradycardia in children.¹⁴ Recent studies suggest a 30% reduction from baseline heart rate can be anticipated and all bradycardia related to dexmedetomidine may not require urgent treatment. Rather, immediate action is required only if bradycardia along with hypotension or serious primary bradyarrhythmia is present.¹⁵ The occurrence of hypotension can be attenuated by pretreatment with balanced salt solution boluses.¹⁶

LIMITATIONS

In addition to a limited sample size, a control group was not used which would have made it easier to compare the findings. The unavailability of depth of anesthesia and end tidal gas monitors also limited the results.

CONCLUSION

This study demonstrates that a premedication dose of Dexmedetomidine in 1µg/kg compared to 0.5µg/kg attenuates the hemodynamic response significantly better from 1 minute to 40 minutes of pneumoperitoneum.

Dexmedetomidine at 1µg/kg required significantly less dose of propofol for induction of anesthesia but had significantly higher incidence of bradycardia compared to 0.5µg/kg.

RECOMMENDATION

Further studies with larger sample size are needed to validate the conclusion. Studies where a premedication dose compared to loading and maintenance dose of dexmedetomidine for hemodynamic changes need to be carried out in search of an ideal adjuvant for general anesthesia during laparoscopic cholecystectomy.

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CONFLICT OF INTEREST

None

FINANCIAL DISCLOSURE

None

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