Role of Intravenous Dexmedetomidine Premedication on Intra-operative Hemodynamics and PONV in Laparoscopic Cholecystectomy

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Abstract

Background: *Laparoscopic cholecystectomy is a gold standard surgical procedure for gallbladder operation. It causes altered hemodynamic responses due to pneumoperitoneum and surgical procedure also causes high incidence of postoperative nausea & vomiting (PONV). Dexmedetomidine has been shown to reduce intraoperative hemodynamic instability and PONV.*

Objective: *This study was designed to evaluate the efficacy of intravenous dexmedetomidine premedication for attenuation of hemodynamic responses associated with pneumoperitoneum & its effect on postoperative nausea &vomiting.*

Methods: *Sixty adult patients of ASA physical status I & II scheduled for elective laparoscopic cholecystectomy were enlisted for a prospective randomized double blind study. They were selected randomized into two equal groups, thirty in each group. Group A received 0.9% normal saline 100 ml & Group B received dexmedetomidine (100µgm) in 100 ml 0.9% normal saline intravenously for 10 minutes before induction of anaesthesia. Pulse rate, mean arterial pressure were recorded prior to induction, 2 minutes after endotracheal intubation, before pneumoperitoneum,10 minutes & 20 minutes after pneumoperitoneum, 10 minutes after release of carbon dioxide(CO_2) & 10 minutes after extubation. In post anaesthetic care unit patient were observed on 2,6,12,24 hour for PONV.*

Results: *Patients in Group B (dexmedetomidine) maintained greater hemodynamic stability compare to Group A after intubation, during pneumoperitoneum and also extubation. Pulse rate & mean arterial pressure significantly varies in Group A compare with Group B at different times of intraoperative period ($p < 0.05$). Postoperative nausea & vomiting was significantly less in Group B (dexmedetomidine).*

Conclusion: *Premedication with intravenous dexmedetomidine (100 µgm) attenuates the hemodynamic responses produced by pneumoperitoneum during laparoscopic cholecystectomy and also significantly reduces nausea and vomiting.*

Keywords: *Dexmedetomidine, laparoscopic cholecystectomy, PONV.*

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Introduction

Laparoscopic cholecystectomy is now a days gold standard treatment option for several gall bladder pathology . Many institute perform it as a day care surgery. It gained worldwide popularity mainly due to much less postoperative pain, small incision, earlier mobilisation, shorter hospital stay and ultimately reduces the economic cost . It was really challenging for the attending anaesthesiologist. Creation of pneumoperitoneum is the symbol for

laparoscopic procedures. The pneumoperitoneum and the patient positions required for laparoscopy bring a lot of physiologic changes that complicate anaesthetic management. Raised IAP (Intra Abdominal Pressure) results in stress hormone response, raised peripheral vascular resistance and reduced cardiac output. Therefore, haemodynamic fluctuation and inadequate organ perfusion may occur[1,2,4,5]. Moreover, insufflation of carbon dioxide causes not only increased sympathomimetic response that expressed as elevated blood pressure and heart rate but also, postoperative nausea and vomiting (PONV) and referred pain to the shoulder [4,5].

An understanding of the pathophysiologic consequences of increased intra-abdominal pressure (IAP) is important for the anaesthesiologist. The effects are compounded by the change in positions. In Trendelenburg position, venous return and cardiac output are increased, whereas central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR) and heart rate are essentially unchanged[2]. In Reverse Trendelenburg position, venous pooling in the lower extremities causes reduced venous return, ejection fraction and cardiac index in addition to decreased left ventricular preload and left ventricular ejection fraction (LVEF) [3].

Carbon dioxide remains as the popular gas for laparoscopic procedures. Significant absorption of carbon dioxide during pneumoperitoneum results hypercarbia and respiratory acidosis. It is well known that hypercarbia and respiratory acidosis has deleterious effects on normal cardiac function especially in compromised ones[4].If it remain untreated causes unexpected hemorrhage ,poor vision and accidental tissue injury.

Postoperative nausea and vomiting is very problematic for the patients and results in discomfort and anxiety which can produce significant morbidity. Furthermore, prolonged period of nausea and vomiting may results in dehydration, electrolyte imbalance and surgical wound rupture[5,6]. Laparoscopic cholecystectomy is associated with a high incidence (53 -72%) of postoperative nausea and vomiting (PONV)[6,7]. The combined effects of the increased intra-abdominal pressure, stretched peritoneum and diffused carbon dioxide into the bowel are responsible for postoperative nausea and vomiting (PONV)[6].

Many mechanical and pharmacological techniques are being used to overcome hemodynamic alteration induced by pneumoperitoneum. Changes in ventilatory setup as mechanical and beta receptor blockers, opioids and magnesium sulphate ($MgSO_4$) as pharmacological agent were used to attenuate these responses, but there is still lack of an ideal drug for this purposes. Increase in tidal volume, respiratory rate , expiratory time and minute volume ultimately increase the excretion of carbondioxide .

Propranolol, a well known beta blocker was studied for control of hemodynamic responses, which showed that it can attenuate pressure response due to CO_2. However, it may produce bradycardia in postoperative period[13]. Although esmolol is an ultra short acting beta-1 blocker which blunt the hemodynamic response to CO_2 pneumoperitoneum, but it needs special instrument for administration and therefore expensive[14]. $MgSO_4$ seems effective but it carries risk of toxicity, such as prolonged neuromuscular blockade[15,17]. Remifentanil can effectively prevent pressure responses associated with pneumoperitoneum[16]. But it is not available now a days in our country.

Those drugs used for preventing hemodynamic changes are not capable of preventing PONV. Therefore, a new drug which can effectively attenuate pressure response and also prevent or reduce PONV associated with laparoscopic cholecystectomy, was being looked for.

Dexmedetomidine is one of the alpha-2 adrenergic agonist that has sedative, analgesic and opioid sparing effects. There was a study that intravenous dexmedetomidine premedication attenuates the haemodynamic responses to laryngoscopy and intubation [18,19,21,24]. Dexmedetomidine was also studied in laparoscopic gynaecological surgery to reduce postoperative nausea and vomiting and was found effective[14].Intravenous dexmedetomidine is very cheap and available in our country. Intramuscular injection is painful, discomfort able to the patient and unreliable in absorption[18,19]. Moreover oral formulation is not available in our country. Where as, premedication with intravenous dexmedetomidine is easy, comfortable, with more patient satisfaction.

Considering all these observations, the present study was designed to evaluate the role of

intravenous dexmedetomidine premedication on intraoperative haemodynamics in laparoscopic cholecystectomy as well as to evaluate it's efficacy in preventing postoperative nausea and vomiting (PONV).

Methods

This randomized prospective clinical study was carried out in the department of Anaesthesiology and SICU, BIRDEM General Hospital, Shahbag, Dhaka. The approval of the Hospital Ethical Committee was properly taken before carrying out the study, informed consent was also taken. Patients aged between 25-50 years and weight between 50-70 kg of both sexes ASA physical status I and II with Mallampati grade I and II scheduled for laparoscopic cholecystectomy. Patient with history of cardiovascular disease like hypertension, ischemic heart disease aortic stenosis, left ventricular failure, arrhythmia , A-V block, history of bronchial asthma, motion sickness, history of nausea & vomiting were excluded from our study. Patient with history of hypersensitivity or reaction with dexmedetomidine also excluded. After recruitment 60 patients were cannulated with 18 gauge intravenous cannula and patients pulse rate, systolic blood pressure, diastolic blood pressure and peripheral oxygen saturation were noted and randomly divided into two groups of 30 patients each. A blinded anaesthesiologist was made responsible for conducting the case irrespective of group allotted to patient. In group A received intravenous 0.9% normal saline 100ml , group B received intravenous dexmedetomidine 100 microgram in 0.9% normal saline 100ml over 10 minutes before induction of anaesthesia.

After proper pre-oxygenation , induction of anaesthesia and endotracheal intubations were done by fentanyl 2µg /kg body weight, propofol 2mg/kg body weight and vecuronium bromide 0.1mg/kg body weight was given as a bolus dose .Ventilation was done with oxygen and halothene1.0 MAC with Bain's circuit. With Macintosh laryngoscope appropriate ETT inserted , fixed on 20 cm in incisor level. Anaesthesia was maintained with oxygen 33% and nitrous oxide 66% with 0.6% halothane. The tidal volume and the ventilatory frequency were adjusted and intermittent positive pressure ventilation (IPPV) was continued to maintain end tidal carbon dioxide between 35–45 mm Hg by capnograph.

Pneumoperitoneum was created by insufflation of carbon dioxide and operation table was tilted to left and about 15° reverse Trendelenburg position. Intra abdominal pressure (IAP) was not be allowed to exceed 14 mm Hg throughout the surgical procedure. After pneumoperitoneum, necessary changes in ventilator setting (tidal volume, respiratory rate, expiratory time) were made to maintain normocapnia. Throughout the procedure, any rise in mean arterial pressure more than 20% from the baseline was treated with labetalol 5mg i/v. Inj. Atropin 0.6 mg i/v when pulse rate Â50 b/min. Monitoring including the systolic, diastolic and mean arterial pressure, pulse rate, SpO2 and end tidal CO2 were recorded at the following points of time: prior to induction, two minutes after endotracheal intubation, before pneumoperitoneum ten minutes after pneumoperitoneum, twenty minutes after pneumoperitoneum, ten minutes after release of carbon dioxide and ten minutes after extubation. At the end of surgery residual neuromuscular blockade was reversed by appropriate dose of neostigmine and atropine intravenously. After extubation patients were transferred to post anaesthetic care unit.

In the postoperative care unit, duty doctor observed for any evidence of post-operative nausea and vomiting in the study patients for 24 hours. On preoperative visit each patient was instructed and demonstrated about the numerical rating scale (NRS) and verbal rating scale (VRS). In the postoperative period number and time of nausea & vomiting was noted and treated with anti-emetic if needed. Grading of nausea was done by verbal 11-point numerical rating scale (NRS), with which the patient was asked to rate severity of nausea between 0 and 10. 0 corresponding to no symptoms and 10 corresponding to worst possible symptoms and categorized as none, mild, moderate and severe. Antiemetics were given to the moderate and severe nauseating patients. Severity of the vomiting was also done by counting the occurrence of vomiting, 1 time was mild, 2 times: moderate and >2 times: severe.

All data were collected in a pre-designed data collection form. Results were compiled and analyzed using students 't' test or Chi square test. P value <0.05 was considered statistically significant. The statistical analysis was done by using software SPSS (Statistical Package for Social Sciences) version 16 and Microsoft excel 2013. And we use web site https://www.graphpad.com/quickcalcs .

Results

Demographic data of patients are shown in Table I. There were no significant differences between the dexmedetomidine and 0.9% normal saline groups regarding age, sex and weight.

Table I *Demographic profile of study group*

Demographic profile	Group – A (0.9% normal saline)	Group-B (Dexmedetomidine)	p-value
Age (years)	30.70±8.12	30.20±10.08	0.840
Weight (Kg)	63.87±7.15	62.65±5.98	0.458
Sex (M : F)	10 : 20	15 : 15	
ASA grading	Grade I = 22	Grade I = 20	
	Grade II = 8	Grade II = 10	0.573 (c2=0. 317)

Values were expressed as mean±SD. Data were analyzed by student's- t test . ASA grading done by chi-square test. Values were regarded as significant if p< 0.05.

Table II *Preoperative vital parameters*

Vital parameters	Group – A (0.9% normal saline)	Group – B (Dexmedetomidine)	p- value
Pulse Rate (bpm)	79.80±10.84	78.00±8.38	0.474
SBP (mm Hg)	120.00±12.20	117.10±12.56	0.368
DBP (mm Hg)	78.80±9.74	77.10±6.61	0.432
MBP (mm Hg)	96.10±9.10	94.80±6.15	0.519

Values were expressed as mean±SD. Data were analyzed by student's t test. Values were regarded as significant if p< 0.05.

The baseline mean pulse rate in Group A (0.9% normal saline) was 79.80±10.84 and in Group B (dexmedetomidine) was 78.00±8.38, where p= 0.405 (Table II). There was no significant difference between the two groups.

Table III *Pulse rate in two groups during intra-operative period*

Pulse rate (bpm)	Group–A (0.9% normal saline)	Group–B (Dexmedetomidine	p-value
Before induction	86.2±9.92	82.90±8.38	0.169
After induction (2 min)	88.70±13.12	80.40±9.64	0.007
Before pneumoperitoneum	76.80±13.67	64.10±6.19	0.001
After pneumoperitoneum (10 min)	82.10±19.10	80.10±7.35	0.594
After pneumoperitoneum (20 min)	74.70±16.99	74.10±7.75	0.600
After release of CO2 (10 min)	76.50±14.93	65.10±7.00	0.000
After extubation (10 min)	87.30±12.44	80.40±5.58	0.007

Values were expressed as mean±SD. Data were analyzed by student's t test. Values were regarded as significant if p< 0.05.

Pulse rate was slower in pre-induction period in the Group B (dexmedetomidine) than in the Group A (0.9% normal saline).

Intra-operative period pulse rate was also slower at each time interval in the dexmedetomidine group in comparison with the 0.9% normal saline group. In the Group A mean pulse rate ranged from 74.70±16.99 to 88.70±13.12, while it ranged between 64.10±6.19 to 82.90±8.38 in the Group B (Table III).

Pulse rate varied significantly at 2 minutes after induction (p= 0.007) ,before pneumoperitoneum(p= 0.001) 10 min After release of CO_2 (p= 0.000) and 10 minutes after extubation (p= 0.007). Pulse rate of two study groups displayed in Fig. 1

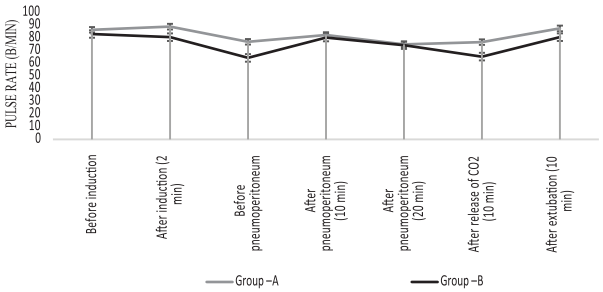

Fig 1 *Variation of pulse rate in two groups during intraoperative period*

Baseline mean blood pressure in Group A (0.9% normal saline) was 93.10±9.10 and in Group B (dexmedetomidine) was 91.80±6.15, where p= 0.519 (Table II). Pre-induction mean blood pressure was significantly lower in the dexmedetomidine group than in the 0.9% normal saline group (p= 0.002).

Intra-operative mean blood pressure was also lower at each time interval in the dexmedetomidine group in comparison with the 0.9% normal saline group.

Mean blood pressure was ranged from 87.87±8.34 to 105.30±8.87 in the Group A 0.9% normal saline) whereas it fluctuated between 85.80±7.38 to 94.50±4.96 in Group B (dexmedetomidine) (Table IV).

Mean blood pressure varied significantly during intra-operative period (p= 0.000). Mean blood pressure of two study groups displayed in Fig. 2.

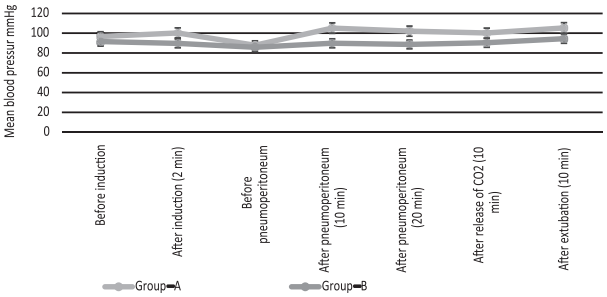

Fig 2 *Variation of mean blood pressure in two groups during intra-operative period*

Table IV *Mean blood pressure in two groups during intraoperative period*

MBP (mm Hg)	Group–A (0.9% normal saline)	Group–B (Dexmedetomidine)	p-value
Before induction	96.60±7.6	91.50±6.63	0.007
After induction (2 min)	100.23±11.66	89.70±7.48	0.000
Before pneumoperitoneum	87.87±8.34	85.80±7.38	0.136
After pneumoperitoneum (10 min)	105.10±8.99	89.80±6.88	0.000
After pneumoperitoneum (20 min)	102.10±5.56	88.70±6.80	0.000
After release of CO_2 (10 min)	100.20±5.30	90.30±7.03	0.000
After extubation (10 min)	105.30±8.87	94.50±4.96	0.000

Values were expressed as mean±SD. Data were analyzed by student's t test. Values were regarded as significant if p< 0.05.

Five patients in the 0.9% normal saline group received inj. labetolol intravenously for the treatment of raised blood pressure. It was not required in the dexmedetomidine group, because they remained hemodynamically stable.

After surgery all patients were sent to the post-operative ward for close observation. During this period the incidences of post-operative nausea and vomiting were recorded. There were 18 incidences of PONV, of which 18 were of nausea and 4 cases were of vomiting.

The incidence of nausea was 46.66% in Group A (0.9% normal saline) and 13.34% in Group B (dexmedetomidine). The difference was statistically significant (p= 0.042) (Table V).

Table V *Incidence of nausea in two groups during postoperative period*

Nausea	Group – A (0.9% normal saline)	Group – B (Dexmedetomidine)	p- value
Mild	5(16.66%)	2(6.66%)	0.042
Moderate	6(20%)	1(3.33%)	
Severe	3(10%)	1(3.33%)	
Not Nauseating	16(53.33%)	26(86.66%)	

Results were expressed in number and percentages in parentheses. Data were analyzed by student's t test and chi-square test. Values were regarded as significant if $p< 0.05$.

In Group A (0.9% normal saline) 16.66% patients had mild, 20% had moderate and 10% had severe nausea. In Group B (dexmedetomidine) 6.67% had mild, 3.33% moderate and3.33% had severe nausea.

The incidence of vomiting was 10% in Group A (0.9% normal saline) and 3.33%in Group B (dexmedetomidine). Severity of vomiting was determined by counting the occurrence of vomiting. The difference was statistically not significant (p= 0254) (Table V) .

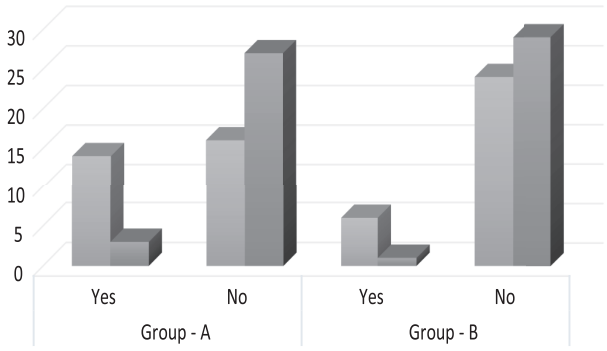

Fig. 3: *Incidences of postoperative nausea and vomiting in two groups*

Table VI *Frequency of vomiting in two groups during postoperative period*

Vomiting	Group – A (0.9% normal saline)	Group – B (Dexmedetomidine)	$\chi 2$- value	p- value
Mild (1 time)	0(0%)	1(3.33%)	4.071	0.254
Moderate (2 times)	2(6.67%)	(0%)		
Severe (>2 times)	1(3.33%)	0(0%)		
No Vomiting	27(90%)	29 (96.67%)		

Results were expressed in number and percentages in parentheses. Data were analyzed by chi-square test. Values were regarded as significant if $p< 0.05$.

Table VII *Use of antiemetic in two groups*

	Group – A (0.9% normal saline)	Group – B (Dexmedetomidine)	$\chi 2$- value	p- value
Needed	9(30%)	1(3.33%)	7.680	0.006
Not Needed	21(70%)	29(96.67%)		

Results were expressed in number and percentages in parentheses. Data were analyzed by chi-square test. Values were regarded as significant if $p< 0.05$.

Antiemetic was needed in 30% patients in Group A (0.9% normal saline) and 3.33% in Group B (dexmedetomidine). The result was statistically significant ($p < 0.05$).

Discussion

Laparoscopic surgeries have become common clinical practices now a days; among these laparoscopic cholecystectomy is the most commonly performed operation. During the laparoscopic cholecystectomy, stress from pneumoperitoneum would make the hemodynamic status of the patient unstable [1-4]. Profound hypertension and alteration of heart rate occurs during carbon dioxide insufflation [6-8]. Pneumoperitoneum along with head up position lead to significant hemodynamic changes – increase in mean blood pressure and systemic vascular resistance and decrease in cardiac output[8]. Pneumoperitoneum also causes increased incidence of postoperative nausea and vomiting. Various studies were done with different techniques and pharmacological agents by various investigators to attenuate these hemodynamic effects of pneumoperitoneum. Separate studies also investigated various drugs and techniques to reduce postoperative nausea and vomiting [13-17]. But still there is lack of a single drug to counteract these effects. Therefore, search for a drug continued, which could effectively attenuate pressure response and also prevent or reduce postoperative nausea and vomiting associated with laparoscopic cholecystectomy.

The present study was conducted in 60 adult patients of ASA physical status I and II, to evaluate the effects of intravenous dexmedetomidine on intraoperative hemodynamics in response to pneumoperitoneum associated with laparoscopic cholecystectomy and also on postoperative nausea and vomiting. Dexmedetomidine is rapidly acting after intravenous administration and onset of action is less then 5 min. Peck effect occur within 15 min and its terminal elimination half life is 2 hour. It is a highly selective á2 adrenergic agonist with sedative, anxiolytic, and analgesic, sympatholytic, and antihypertensive effects. Activation of á2 adrenergic receptors in the brain and spinal cord inhibits neuronal firing leading to hypotension, bradycardia [19]. In this study, 100 µg dexmedetomidine was administered intravenously 10 minutes before the beginning of laparoscopic cholecystectomy.

In our study, though normocapnia was maintained by changing the ventilator mood , there was rise in pulse rate and mean arterial pressure in Group A (those who receiving 0.9% Normal saline). But both were more stable and maintained around baseline reading following premedication with intravenous dexmedetomidine. thios study is also comparable with the study conducted by authors Bhattacharjee DP et al. and Keniya VM et al. [20,21]

It produces sedation and anxiolysis by binding to alpha 2 receptors in the locus ceruleus thereby diminishing the release of noradrenaline and inhibiting the sympathetic activity .Thus it decreases the pulse rate and the blood pressure [18,19].

In our study pulse rate were significantly varied in Group A (0.9% Normal saline) compared with Group B (dexmedetomidine) after induction and before pneumoperitoneum. That was comparable with Suliman et al. [23]. They found that dexmedetomidine at a dose 0.5mcg/kg as 10 min infusion prior to induction of general anaesthesia attenuates sympathetic response to laryngoscopy and intubation in patients undergoing myocardial revascularization. We have found significant change of pulse rate 10 min after release of CO2 and after extubation. That was also comparable with Barkha et al. [24]. In their study they found that heart rate, systolic ,diastolic and mean blood pressure significantly ($p < 0.001$) raised in control group than the dexmedetomidine group at the time of extubation. That study dexmedetomidine 0.75 mcg/kg which was administered 15 min before extubation.

Our study is also comparable with the study of Vinayak et al.[22] Vora KS et al.[26]. They infused dexmedetomidine 15 minutes before operation in one group found significant reduction of blood pressure in both groups.

In our study Group B (dexmedetomidine) suffered significantly (pÂ 0.05) less mean blood pressure with Group A (0.9% Normal saline). It was compare with the study done by Bhattacharjee DP et al. [20], Barkha Bindu et al. [25], Vora KS et al.[26].

In our study, we did observe episode of bradycardia intraoperatively in two patients of dexmedetomidine group and were treated by injecting injection atropine 0.6 mg intravenously. None of the patient in the NS group had bradycardia. Possible reason for such a low incidence rate of bradycardia might be due to slow infusion of bolus. [22, 26].

In our study Group B (dexmedetomidine) suffered significantly (p= 0.039) less postoperative nausea and vomiting compared with Group A (0.9% Normal saline). This finding is comparable with the study of Bakri et al. [27] In their study they used dexmedetomidine and compare it with dexamethasone and found significant (p= 0.021) effects in reducing postoperative nausea and vomiting. Our study is also comparable with the meta analysis done by Xiao et al. [28] They used intravenous dexmedetomidine and compared with placebo and found superiority of dexmedetomidine and this is due to reduced opioids consumption . It was documented by Ohtani et al. [29] , that perioperative infusion of dexmedetomidine at high dose reduces post- operative analgesic requirements .

Our study also matched with Massad IM et al. [30]. As they added dexmedetomidine to other anesthetic agent and found a significant drop of postoperative nausea and vomiting after laparoscopic gynecological surgeries. Thus it appears that dexmedetomidine is an appropriate premedication in laparoscopic cholecystectomy to fulfill the anaesthetic aims of reducing stress response and subsequent adverse effects. Intravenous dexmedetomidine easily available and cheaper in our country.

Our study concluded that intravenous dexmedetomidine premedication in laparoscopic cholecystectomy cases provided stable haemodynamics during intraoperative period and also reduced postoperative nausea and vomiting. Hence it can be recommended as a routine premedication for laparoscopic cholecystectomy. However further study is recommended to find out its efficacy in patient with compromised cardiovascular system, and with a larger sample size.

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