Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 7
Open Access

Comparison of Perioperative Hemodynamic Responses of Intravenous Dexmedetomidine and Esmolol Carbon Dioxide Pneumoperitoneum During Laparoscopic Surgery

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Cite this paper as: Mohammad Mominul Haque, Mehedi Masud, Nasima Sultana, Md. Hasanuzzaman, Md. Kamrul Hasan, Most. Lubna Mariom, A. K. Al Miraj, (2024). Comparison of Perioperative Hemodynamic Responses of Intravenous Dexmedetomidine and Esmolol Carbon Dioxide Pneumoperitoneum During Laparoscopic Surgery. *Frontiers in Health Informatics*, *Vol.13(7) 1672-1678*

ABSTRACT

Background: Laparoscopic surgery has many advantages, including less blood loss, smaller incisions, less pain, shorter recovery time, and less exposure of internal organs to possible external contamination, thereby reducing the risk of infection. Carbon dioxide pneumoperitoneum during laparoscopic surgery increases arterial pressure, heart rate, and systemic vascular resistance.

Methods: This prospective randomized study was conducted from July 2023 to August 2024 after taking approval by the Institutional Ethics Committee of BSMMU Dhaka, Bangladesh and written informed consent from the patients. 60 patients of both sexes undergoing elective laparoscopic cholecystectomy were randomly divided into three groups of 20 patients each. Group A received a 500 mcg/kg bolus of esmolol before pneumoperitoneum followed by an infusion of 100 mcg/kg/min. Group B received a 1 µg/kg intravenous bolus of dexmedetomidine before pneumoperitoneum followed by an infusion of 0.2 µg/kg/h. Group C (control) received 0.9% saline.

Results: Sixty patients, of either sex undergoing elective laparoscopic cholecystectomy, were randomly allocated into three groups containing twenty patients each. The patients allocated into the Group A, Group B, and Group C was comparable with respect to age, distribution of gender, body weight, and the duration of surgery. No significant difference was found regarding the preoperative MAP and the MAP values following intubation and before pneumoperitoneum among all three groups (P >0.05). Mean arterial pressure and HR in Group A and D were significantly less throughout the period of pneumoperitoneum in comparison to Group C. IV nitroglycerine was required in 45% (9 out of 20) patients in Group C to control intraoperative hypertension, and it was clinically significant in comparison to Group A and D.

Conclusion: In conclusion, both esmolol and dexmedetomidine effectively reduce the increase in MAP and HR during and after pneumoperitoneum, thereby providing hemodynamic stability during laparoscopic surgery. There is no significant difference between the efficacy of esmolol and dexmedetomidine in reducing the hemodynamic response to pneumoperitoneum or laparoscopic surgery.

Keywords: Dexmedetomidine, Esmolol, Hemodynamics, Laparoscopic Surgery, Pneumoperitoneum.

INTRODUCTION

Laparoscopic surgery has many advantages, including less blood loss, smaller incisions, less pain, shorter recovery time, and less exposure of internal organs due to possible external contamination, thereby reducing the risk of infection. However, it is not without drawbacks. Increased intraperitoneal pressure and volume (pneumoperitoneum), the patient's extreme position (reverse Trendelenberg position), and carbon dioxide accumulation have a strong impact on the patient's hemodynamic, respiratory, and metabolic functions [1,2]. To mitigate these reactions, various technical improvements have been attempted. Various drugs, such as nitroglycerin [3], beta-blockers [4], opioids [5], gabapentin [6], pregabalin [7], magnesium sulfate [8], clonidine [9], and dexmedetomidine [10], are used concomitantly with varying success rates to ensure hemodynamic stability during pneumoperitoneum. To avoid these drawbacks, we added two adjuvants in the perioperative period, namely esmolol and dexmedetomidine, and observed their effects on intraoperative hemodynamics. Dexmedetomidine is a highly selective α2-adrenergic receptor agonist that dose-dependently reduces blood pressure and heart rate and has sedative and analgesic properties without activating α1-receptors. It also reduces sympathetic nervous system activity via the central nervous system, thereby reducing hemodynamic and plasma catecholamine responses to stressful events during surgery. However, its role in modern intraoperative anesthesia practice is still unclear, and there are few studies on human cardiovascular parameters during perioperative continuous infusion of drugs in laparoscopic surgery. However, the creation of a pneumoperitoneum has its own disadvantages, including: B. Adverse effects on hemodynamics, cardiovascular system, respiration, stress response, and acid-base physiology. Increased release of vasopressin, catecholamines, or both is responsible for these hemodynamic responses [2, 3, 4]. Dexmedetomidine inhibits the release of catecholamines and vasopressin, thereby modulating the hemodynamic changes induced by pneumoperitoneum [11-13]. Although these complications are less severe in ASA I and II patients, exaggerated responses to pneumoperitoneum have been reported in older patients and in ASA III patients, especially in those with impaired cardiovascular physiology. The control and correction of these hemodynamic changes has opened a whole new chapter in the field of anesthesia. However, its role in modern intraoperative anesthesia practice has yet to be established, and there are few studies on human cardiovascular parameters during perioperative continuous infusion of drugs in laparoscopic surgery. Esmolol is the first intravenously titratable β-blocker available for use in the surgical setting. It is a cardioselective β1-receptor blocker with a fast onset of effect, a very short duration of action, and no significant intrinsic sympathomimetic or membrane-stabilizing effects at therapeutic doses. In addition to its effects on the sympathetic nervous system, esmolol also influences important components of anesthesia therapy, such as analgesia, hypnosis, and memory function [12, 13]. It is a class II antiarrhythmic drug, and its sympatholytic action reduces norepinephrine secretion, lowering mean arterial pressure (MAP) and heart rate (HR).

MATERIALS & METHODS

This prospective randomized study was conducted from July 2023 to August 2024 after taking approval by the Institutional Ethics Committee of BSMMU Dhaka, Bangladesh and written informed consent from the patients. A total of 60 patients aged 20–60 years with American Society of Anesthesiologists (ASA) grades I and II undergoing elective laparoscopic cholecystectomy under general anesthesia were randomly assigned to one of three groups of 20 patients each: group A (esmolol group), group B (dexmedetomidine group) and group C (control group). Power calculations suggested that at least 17 patients per group were needed to detect a 10% difference in arterial pressure between the groups (a = 0.05, b = 0.80), taking into account possible dropouts. Thus, 20 patients from each group were included in the study. Patients who could not complete the surgery laparoscopically and underwent open cholecystectomy were excluded from the study.

Patients with preexisting hypertension, bronchial asthma, diabetes, sinus bradycardia, and severe hepatic, renal, endocrine and cardiac dysfunction were excluded from the study. Patients were then randomly allocated (using computer-derived random number sequence) into three groups (n = 20) to receive one of the following regimens: Group A received bolus dose of 500 µg/kg intravenous (IV) esmolol before pneumoperitoneum followed by an infusion of 100 µg/kg/min. Group B received bolus dose of 1 µg/kg IV dexmedetomidine before pneumoperitoneum followed by infusion of 0.2 µg/kg/h. Group C received saline 0.9%.

All the patients were given diazepam 10 mg and ranitidine 150 mg orally on the night before surgery and tablet ranitidine was repeated on the morning of surgery. On arrival to operation theater, routine ASA monitoring (electrocardiography, pulse oximetry, and noninvasive blood pressure) was started and baseline vital parameters, for example, HR, MAP, and arterial oxygen saturation were recorded. An IV line was started. Patients were induced with fentanyl 2 µg/kg and propofol 2 mg/kg intravenously (IV). Endotracheal intubation was facilitated by muscle relaxant rocuronium 0.7 mg/kg. Anesthesia was maintained with 33% O_2 in N_2O, 0.6% isoflurane, and intermittent bolus dose of rocuronium. Patients received additional doses of fentanyl 1 µg/kg (IV) at half hourly intervals. Group A patients received bolus dose of 500 µg/kg IV esmolol before pneumoperitoneum followed by an infusion of 100 µg/kg/min. Group B received bolus dose of 1 µg/kgIV dexmedetomidine before pneumoperitoneum followed by infusion of 0.2 µg/kg/h and those allocated in Group C received 0.9% saline. CO_2 was insufflated into the peritoneal cavity to create pneumoperitoneum. Intra-abdominal pressure (IAP) was

maintained up to 12 mmHg throughout the laparoscopic procedure. All the patients were positioned in a head-up tilt of 15°. The patients were mechanically ventilated to keep end-tidal CO_2 between 35 and 45 mmHg. Injection paracetamol 1000 mg was infused IV in every patient. Patients were observed for adverse events, for example, bradycardia, hypotension, and hypertension during postoperative period in postanesthesia care unit.

Statistical analysis: The numerical data obtained from the study were expressed as mean ± standard deviation comparison between groups were performed with Kruskal–Wallis one-way analysis of variance by ranks or Fisher's exact test for small samples with a 5% risk. Mann–Whitney– Wilcoxon tests were performed when normality tests failed (All analyses were performed on SPSS software (windows version 23.0).

RESULTS

A total of 60 patients aged 20–60 years with undergoing elective laparoscopic cholecystectomy under general anesthesia were randomly assigned to one of three groups of 20 patients each. The patients allocated into the Group A, Group B, and Group C was comparable with respect to age, distribution of gender, body weight, and the duration of surgery (Table 1). No significant difference was found regarding the preoperative MAP and the MAP values following intubation and before pneumoperitoneum among all three groups ($p>0.05$. However, following pneumoperitoneum, MAP values in Group A and Group B were significantly lower compared to Group C at 10, 20, 30, 40, and 50 min after pneumoperitoneum, following the release of CO_2 and after extubation ($p<0.05$). On comparing patients in Group A and Group B, no significant difference in MAP was found at any time interval. Similarly, no significant difference was found between the preoperative HR, and the HR values following intubation and before pneumoperitoneum among all three groups ($P > 0.05$) (Table 2). However, following pneumoperitoneum, HR values in Group A and Group B were significantly lower compared to Group C at 10, 20, 30, 40, and 50 min after pneumoperitoneum, following the release of CO_2 and after extubation ($p<0.05$) (Table 3). On comparing patients in Group A and Group B, no significant difference in HR was found at any time interval. Three patients of Group A and two patients of Group B suffered from bradycardia in our study, but the incidences are not statistically significant. Hypertension occurred in nine patients (45%) of Group C, whereas no patients of Group A and B suffered from hypertension. There was no incidence of hypotension in any group (Table 4). Comparison of systolic and diastolic blood pressure showed no statistically significant difference between two groups (Table-5). When the groups were compared for the parameters of recovery-extubation time, response to verbal commands, and time for orientation, there were no significant differences among the groups ($p> 0.05$) (Table 6 & 7).

Table 1: Patient's characteristics and duration of surgery (mean±SD) (N=60)

	Group A **(n=20)**	Group B **(n=20)**	Group C **(n=20)**	p value
Age (years)	28.4±5.12	31.4±5.36	30.4±5.24	0.45
Sex (male/female)	8/12	9/11	8/12	
Weight (kg)	45.24±8.16	46.4±8.26	47.88±9.4	0.51
Duration of surgery (min)	45.4±6.24	46.4±8.26	44.36±5.26	0.54

Table 2: Changes in mean arterial pressure (N=60)

	Group A	**Group B**	**Group C**	**p value**
Preoperative	88.4±8.6	89.32±6.8	87.22±6.4	0.69
After intubation	100.4±10.6	102.4±11.2	103.32±12.6	0.70
Before pneumo- peritoneum (PP)	97.6±10.8	98.6±11.24	96.8±9.4	0.83
10 min after PP	95.4±8.4*	96.2±8.6*	106.42±10.6	0.0005
20 min after PP	96.6±11.6*	94.4±10.6*	108±12.6	0.0005
30 min after PP	94.6±10.6*	93.6±9.6*	106.4±11.6	0.0003
40 min after PP	93.6±11.8*	94.4±10.6*	107.2±10.4	0.0002
50 min after PP	95.6±9.6*	94.6±11.4*	108.24±12.6	0.0003
After release of PP	90.4±9.2*	89.32±8.4*	101.8±11.4	0.0003
After extubation	94.8±10.36*	92.8±9.4*	104.6±10.6	0.0008

Table 3: Changes in heart rate (mean±SD) (N=60)

	Group A	**Group B**	**Group C**	**p value**
Preoperative	80.2±6.3	81.2±4.2	81.34±4.6	0.77
After intubation	97.6±10.44	98.2±9.6	100.2±11.6	0.78
Before pneumo- peritoneum (PP)	86.6±9.4	87.2±8.6	88.4±8.8	0.92
10 min after PP	78.2±8.8*	80.4±6.8*	93.4±11.4	0.0001
20 min ater PP	80.4±10.4*	79.2±8.2*	94.8±11.6	0.0001

30 min after PP	81.6±9.4*	79.6±7.2*	96.8±10.4	0.0001
40 min after PP	82.6±8.4*	81.8±8.2*	97.6±11.4	0.0001
50 min after PP	81.4±9.4*	79.6±7.2*	96.8±10.4	0.0001
After release of PP	79.4±9.6*	81.4±8.6*	90.2±10.4	0.0013
After extubation	85.2±10.4*	84.4±9.6*	98.84±11.6	0.0001

Table 4: Systolic blood pressure (SBP) (N=60)

	Group A	**Group B**	p value
Preoperative	122.90±14.47	122.06±14.63	0.773
After intubation	125.90±13.64	126.80±14.14	0.747
Before pneumo- peritoneum (PP)	124.90±13.63	126.28±13.50	0.612
After10 minutes	124.90±13.63	126.28±13.50	0.612
After 20 minutes	119.50±10.09	117.50±9.45	0.309
After 30 minutes	118.64±9.28	116.96±9.49	0.375
After 40 minutes	109.90±9.10	108.42±8.80	0.483
After50 minutes	119.21±10.87	116.75±10.55	0.453
After release of pneumoperitoneum	124.04±8.62	122.78±7.90	0.448
After extubation	137.70±14.17	136.26±14.40	0.615

Table 5: Diastolic blood pressure (DBP) (N=60)

Time interval	**Group A**	**Group B**	p value
Preoperative	71.96±12.88	70.40±13.15	0.555
After intubation	79.34±11.11	79.12±11.41	0.922
Before pneumo- peritoneum (PP)	77.60±11.13	78.28±11.21	0.761
After10 minutes	87.56±11.23	86.60±10.78	0.644
After 20 minutes	87.56±11.23	86.60±10.78	0.664
After 30 minutes	82.50±11.67	79.92±11.06	0.259
After 40 minutes	79.90±8.54	78.78±8.18	0.505
After50 minutes	76.54±10.43	73.27±10.52	0.817
After release of pneumoperitoneum	79.33±11.32	75.30±8.90	0.203
After extubation	83.52±8.24	81.96±7.36	0.321

Table 6: Distribution of patients according to adverse effects (N=14)

Adverse effects	Group A	Group B	Group C
Bradycardia	3	2	0
Hypotension	0	0	0
Hypertension	0	0	9

Table 7: Recovery time (minutes) (mean±SD) (N=60)

	Group A	**Group B**	**Group C**	**p value**
Extubation time	6.56±1.42	7.12±1.64	6.72±1.6	0.57
Response to verbal command	7.62±1.34	7.92±1.6	7.82±1.4	0.63
Time for orientation	8.96±1.44	9.12±1.62	8.84±1.76	0.67

DISCUSSION

The use of perioperative dexmedetomidine and esmolol infusion during laparoscopic cholecystectomy was observed to maintain better hemodynamic stability compared to the control group. Esmolol showed lower blood pressure and heart rate fluctuations (compared to the control group) due to attenuation of sympathetic stimulation, but the response of the dexmedetomidine group was better across all time intervals. Srivastava VK et al. in their study emphasized the use of dexmedetomidine and esmolol to reduce the hemodynamic response to pneumoperitoneum in laparoscopic cholecystectomy and concluded that dexmedetomidine can prevent such hemodynamic responses in laparoscopic surgery more effectively than esmolol. Their results are similar to those of the present study. In addition, dexmedetomidine and esmolol also reduce the induction dose of propofol and the requirement of intraoperative fentanyl. [14] Patients divided into Group A, Group B, and Group C were comparable in terms of age, gender distribution, weight, and operation time. This study observed and compared the effects of esmolol and dexmedetomidine administered before pneumoperitoneum on hemodynamics in patients undergoing laparoscopic cholecystectomy. In laparoscopic surgery, CO2 is routinely used to create pneumoperitoneum. [5, 6] Immediately after pneumoperitoneum, plasma levels of catecholamines and vasopressin increase. No significant differences were found in preoperative MAP values, MAP values after

intubation, and before pneumoperitoneum among all three groups (P> 0.05). However, after pneumoperitoneum, MAP values in Group A and Group B were significantly lower than those in Group C at 10, 20, 30, 40, and 50 minutes after pneumoperitoneum, after CO_2 delivery, and after extubation (P < 0.05). Elevated catecholamine levels activate the renin-angiotensin-aldosterone system, resulting in characteristic hemodynamic changes such as increased arterial pressure and increased systemic/pulmonary vascular resistance.[8, 9] Vasopressin also contributes to the increase in arterial pressure by increasing systemic vascular resistance.[6] Agents such as α2-adrenergic agonists[15,16] and magnesium sulfate[17] have been successfully used to attenuate the increase in MAP and HR in response to pneumoperitoneum during laparoscopic surgery. Esmolol is an ultra-short-acting, cardiac-selective α1-adrenergic receptor antagonist that has been shown to be effective in attenuating adrenergic responses to noxious stimuli during the perioperative period. [18,19] Esmolol has been successfully used for endotracheal intubation, [20] maintenance of anesthesia,[19] emergence from anesthesia, and extubation.[18] It has also been used to blunt blood pressure and heart rate responses to noxious stimuli. The hemodynamic effects of esmolol are thought to be mediated by blockade of peripheral beta-adrenergic receptors. [21] used an initial bolus dose of esmolol of 1 mg/kg before pneumoperitoneum, followed by an infusion of 200 μg/kg/min. They found that esmolol was effective in reducing increases in heart rate and arterial pressure during laparoscopic surgery. [21] At our institution, we have tried similar doses of esmolol (both bolus and infusion) but found the incidence of bradycardia to be unacceptably high. The recommended bolus dose of esmolol varies between 250 mcg/kg and 1 mg/kg, with infusion rates ranging from 50 to 300 mcg/kg/min. Thus, in our study, we administered an intravenous bolus of 500 mcg/kg of esmolol before pneumoperitoneum, followed by an infusion of 100 mcg/kg/min, and found that the dose was still effective. Dexmedetomidine is an α2-adrenergic receptor agonist that has hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties without causing significant respiratory depression. [22] Activation of the receptors in the brain and spinal cord inhibits neuronal activity, thereby causing hypotension, bradycardia, sedation, and analgesia. [23] Presynaptic activation of α2-adrenergic receptors inhibits the release of norepinephrine. Postsynaptic activation of α2-adrenergic receptors inhibits sympathetic outflow and therefore reduces blood pressure and heart rate. [24] Dexmedetomidine does not appear to have a direct effect on the heart.[25] Bhattacharjee et al [16] used dexmedetomidine at a bolus dose of 1μg/kg IV before pneumoperitoneum, followed by an infusion of 0.2μg/kg/h. They found that dexmedetomidine effectively attenuated the negative hemodynamic response to CO2 pneumoperitoneum. [16] In our study, we administered this dose of dexmedetomidine to patients in group B. MAP in the esmolol group was at several time intervals of pneumoperitoneum. H. was higher than that in the dexmedetomidine group at 30, 40, and 50 minutes after pneumoperitoneum, and after the pneumoperitoneum had resolved. However, esmolol may also provide better hemodynamic stability than dexmedetomidine, as MAP in the esmolol group was not below 20% of baseline in any of the observational data. This type of effect of esmolol has been reported by various researchers, such as Ozturk T [26], Collard et al. [27], Ibrahim et al. [28], and Srivastava V et al. [29]. The limitations of this study were that the dose of propofol, the requirement of fentanyl during surgery, and the sedation level were not analyzed in this study. The sample size of the study was small and was conducted at only one center; therefore, it is not representative of the entire population. In our study, baseline MAP and MAP after intubation and before pneumoperitoneum were comparable among the three groups. However, patients in groups A and B had significantly lower MAP during the period of CO2 pneumoperitoneum and after extubation compared with patients in group C. Similar results were observed in the case of HR. Thus, both esmolol and dexmedetomidine administered intravenously before and during pneumoperitoneum were effective in attenuating the increase in MAP and HR during CO2 pneumoperitoneum. Diamond et al. [30] reported a 35-fold increase in cardiac output in dogs with an elevated IAP of 40 mmHg. Ishizaki et al. [31] attempted to determine a safe IAP during laparoscopic surgery. Regarding side effects, in our study, none of the patients in the two groups suffered from hypotension or bradycardia. Nine patients (45%) in group C developed hypertension requiring treatment with nitroglycerin infusion, while no patients in groups A and D suffered from hypertension. They concluded that dexmedetomidine is an effective anesthetic adjuvant that can be safely used in laparoscopy without the fear of losing consciousness under anesthesia. [32] Coloma et al. suggested that perioperative esmolol is an effective alternative to remifentanil in gynecological laparoscopic surgery. They also observed that esmolol plays a role in maintaining hemodynamic stability during the intraoperative period of laparoscopic cholecystectomy. [33]

CONCLUSION

In conclusion, both esmolol and dexmedetomidine effectively reduce the increase in MAP and HR during and after pneumoperitoneum, thereby providing hemodynamic stability during laparoscopic surgery. There is no significant difference between the efficacy of esmolol and dexmedetomidine in reducing the hemodynamic response to pneumoperitoneum or laparoscopic surgery.

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