Research Article

Comparative study of clonidine versus esmolol on hemodynamic responses during laparoscopic cholecystectomy

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Abstract *Background:* Laparoscopic surgical procedures have various benefits to the patient in terms of decreased tissue damage, early ambulation, decreased hospital stay and reduced analgesic needs. Pneumoperitoneum with carbon dioxide (CO_2) leads to stimulation of the sympathetic nervous system which can be a risk factor in patients with cardiovascular diseases. Moreover, reverse Trendelenburg position affects homeostasis in laparoscopic surgeries. In this study, we compared the efficacy of clonidine (which is $\alpha 2$ adrenergic agonist) versus esmolol (which is ultra short acting cardio-selective $\beta 1$-receptor antagonist) on the hemodynamic response during laparoscopic cholecystectomy.
Materials and methods: A total of 60 patients scheduled to undergo laparoscopic cholecystectomy were randomly assigned into two groups: Group C: received 2 µg/kg of clonidine diluted in 20 ml normal saline, given with slow intravenous infusion over 10 min just before induction of GA and Group E: received 1.5 mg/kg of esmolol as a loading dose over a period of 5 min just before induction of GA followed by 10 µg/kg/min as a maintenance dose throughout the procedure. No hypnotic medication was given on the evening before surgery. Systolic, diastolic, mean arterial blood pressures and heart rate were recorded at (1) baseline, (2) three minutes after endotracheal intubation, (3) before pneumoperitoneum, (4) fifteen minutes after pneumoperitoneum, (5) thirty minutes after pneumoperitoneum, (6) five minutes after release of CO_2 and (7) five minutes after extubation. Degree of sedation according to Ramsay sedation score was assessed 15 min after reaching PACU.
Results: Both groups were similar with respect to demographic data. Clonidine group showed more stability in hemodynamic responses than esmolol group in all hemodynamic variables but with more postoperative sedation.
Conclusion: This study concluded that clonidine and esmolol provide hemodynamic stability in laparoscopic cholecystectomy but clonidine provides more stability with postoperative sedation.

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1. Introduction

Laparoscopy has now become the standard technique of choice for cholecystectomy. Laparoscopic surgical procedures have various benefits to the patient in terms of decreased tissue damage, early ambulation, decreased hospital stay and reduced analgesic needs. The hallmark of laparoscopy is the creation of pneumoperitoneum with carbon dioxide (CO_2) which leads to stimulation of the sympathetic nervous system resulting in pathophysiological changes characterized by increase in arterial pressure and systemic and pulmonary vascular resistance (SVR and PVR) early after the beginning of intra-abdominal insufflation with little change in heart rate (HR) which can be a risk factor for adverse cardiologic events in patients with pre-existing essential hypertension, ischemic cardiac disease, or increased intra-cranial or intra-ocular pressure [1–4]. Moreover, there is a significant change in the homeostasis observed in reverse Trendelenburg position used for laparoscopic surgeries. In addition, the anesthetic agents put together alter the cardiopulmonary function significantly [5].

Different pharmacological agents such as α2 adrenergic agonists, magnesium sulfate [6], beta-blockers [7] and opioids [8] are used to attenuate circulatory response due to pneumoperitoneum. Clonidine is a selective α2 adrenergic agonist which causes fall in blood pressure and heart rate (HR) with decreased SVR and cardiac output [9]. Esmolol, an ultra short-acting cardio-selective β1-receptor antagonist, has been shown to blunt hemodynamic responses to perioperative noxious stimuli [10]. Hence, the present randomized study was designed to evaluate and compare the efficacy of clonidine versus esmolol on hemodynamic response during laparoscopic cholecystectomy. In other words, the rationale of the study was to reach laparoscopic cholecystectomy with stable hemodynamics.

2. Materials and methods

This was a randomized, double blind, comparative clinical study performed in Ain shams University Hospitals from November 2014 till May 2015. After getting approval from the institutional ethical committee, an informed consent was taken from every patient enrolled in the study.

Sixty patients aged $\geqslant 20$–$\leqslant 60$ years, ASA physical status I or II, planned for elective laparoscopic cholecystectomy were included. The exclusion criteria included the following: ASA physical status > 2, taking beta-blocking drugs or sedatives or antihypertensives or antipsychotics or analgesics, inability to communicate with the patient due to any reason, patients with neurologic, cardiovascular, renal, hepatic diseases or diabetes mellitus, pregnant or breast-feeding females, duration of procedure lasting for more than 120 min and anticipated difficult airway.

2.1. Method of randomization

Patients were allocated randomly by a computer generated list of random permutations to one of two equal groups (30 patients each): group C and group E.

– Group C: Received 2 µg/kg of clonidine diluted in 20 ml normal saline, given with slow intravenous infusion over 10 min just before induction of GA.
– Group E: Received 1.5 mg/kg of esmolol as a loading dose over a period of 5 min just before induction of GA followed by 10 µg/kg/min as a maintenance dose throughout the procedure.

Randomization sequence was concealed in sealed envelopes performed by the help of an independent personnel. An appropriate code number was assigned to each patient, with an allocation ratio of 1:1. The study solutions were prepared and injected by an attending anesthesiologist who was not involved in the patient care or data collection. All patients, investigators and anesthesiologists were blinded to the infusion administered. Drug administration and data collection were carried out by investigators in a double-blind manner.

No hypnotic medication was given on the evening before surgery. Patients were premedicated with glycopyrrolate 0.02 mg/kg i.v. and ondansetron 4 mg i.v. in the preoperative room. Upon arrival in the operating room, monitors were attached to the patients and baseline parameters (heart rate, NIBP, oxygen saturation, temperature and end tidal CO_2, and ECG) were recorded.

After pre-oxygenation with O_2 100% for 3 min, anesthesia was induced with a standard anesthetic protocol using midazolam 0.03 mg/kg, fentanyl 1 µg/kg, thiopentone sodium 3–5 mg/kg, and tracheal intubation was facilitated by atracurium 0.5 mg/kg intravenously. Lungs were mechanically ventilated with O_2 50% and anesthesia was maintained with isoflurane 0.8% and atracurium 0.1 mg/kg every 25 min. Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide [$EtCO_2$] 40 ± 5 mmHg). Pneumoperitoneum was created by insufflations of CO_2 and operation table was tilted to about 15° reverse Trendelenberg. Intra-abdominal pressure was not allowed to exceed more than 14 mmHg. After 1 h of surgery, each patient received 1 g paracetamol infused over 30 min intravenously. During surgery, Ringer's lactate solution was administered in maintenance dose as per Holliday-Segar formula. Any hypotension (MAP < 20% preoperative) was managed with a fluid bolus of normal saline 250–300 ml. If hypotension did not respond to fluid administration, then ephedrine 15 mg i.v. was ready to be administered. Any incidence of bradycardia (HR < 50/min) was treated with atropine 0.7 mg i.v.

At the end of surgery, residual neuromuscular block was reversed by the injection of neostigmine 0.05 mg/kg and glycopyrrolate 0.02 mg/kg i.v. and patient was extubated when respiration was sufficient, and they were able to obey commands. Esmolol infusion was stopped 5 min after extubation. Patients were transferred to the postanesthesia care unit (PACU) where they were monitored for any evidence of complications or adverse events. Systolic, diastolic, mean arterial blood pressures and heart rate were recorded at the following points of time:

(1) Prior to induction before receiving clonidine or esmolol (baseline).
(2) Three minutes after endotracheal intubation.
(3) Before pneumoperitoneum.
(4) Fifteen minutes after pneumoperitoneum.

(5) Thirty minutes after pneumoperitoneum.
(6) Five minutes after release of CO_2.
(7) Five minutes after extubation.

Degree of sedation according to Ramsay sedation score was assessed 15 min after reaching PACU. Level of sedation score was as follows: 0 Awake and agitated 1 Awake and comfortable 2 Asleep and arousable 3 Asleep with sluggish response to verbal commands or touch 4 No response to verbal command or touch. The results obtained in the study are presented in tabulated manner.

The primary outcomes of our study were as follows: systolic blood pressure, diastolic blood pressure, mean blood pressure and heart rate. The secondary outcomes were as follows: postoperative sedation and any possible side effects of the 2 drugs.

2.2. Statistics

Statistical presentation and analysis of the present study were conducted, using the mean, standard deviation, Chi-square, paired *t*-test and unpaired *t*-test by **SPSS V17**. Unpaired Student *T*-test was used to compare between related samples.

Fisher's exact test and Yates' corrected chi-square are computed for 2×2 tables.

2.3. Sample size

The sample size was calculated using Epicalc 2000 software depending on the results from previous studies [6,7] with the following parameters:

Type I error (α) = 5% with confidence level 95% and power of study 90% (power of test) with type error II 10% (Beta) with expected difference of 0.36. The minimal sample size was 28 in each group. A total of 30 patients in each group were included to compensate for possible dropouts. Corresponding *P* was computed. $P < 0.05$ was considered as statistically significant.

3. Results

There were no significant differences between the two groups with regard to demographic data such as age, sex, weight and ASA grade (Table 1).

Preoperative vital data before induction (SBP, DBP, MBP and HR) were compared between the two groups of patients and no significant difference was found (baseline values of Tables 2–5). Systolic arterial pressure, diastolic blood pressure and mean blood pressure increased slightly after intubation in both groups and then decreased significantly intraoperatively and after extubation compared to baseline values but it was significantly lower in group C compared with group E (Tables 2–4) and (Figs. 1–3). One patient suffered from significant hypotension in group C which was managed with a fluid bolus of normal saline 300 ml and ephedrine 15 mg i.v.

After intubation and till 5 min after extubation, mean HR values measured were significantly lower in group C compared to group E and in both groups the values were lower than baseline values except in group E 3 min after intubation (mean value was slightly higher than baseline value) (Table 5 and Fig. 4).

2 patients in group C required intravenous atropine due to bradycardia (HR < 50).

Table 1 Demographic data.

	Group C (n = 30)	Group E (n = 30)	Tests X^2/t	P-value
Sex				
Female	22(73.3%)	24(80%)	0.373	0.542
Male	8(26.7%)	6(20%)		
Age				
Mean ± SD	43.63 ± 4.46	45.20 ± 4.96	1.287	0.203
Weight				
Mean ± SD	71.53 ± 7.98	73.03 ± 8.09	0.723	0.472
ASA				
I	19(63.3%)	17(56.7%)	0.278	0.598
II	11(36.7%)	13(43.3%)		

Table 2 Changes in systolic arterial pressure.

SBP	Groups		T-test	
	Group C (n = 30) Mean ± SD	Group E (n = 30) Mean ± SD	t	P-value
Baseline	119.77 ± 3.51	118.40 ± 2.62	1.713	0.092
3 min after intubation	122.23 ± 2.19	127.90 ± 1.63	11.371	<0.001*
Before pp	115.20 ± 2.66	121.57 ± 1.98	10.528	<0.001*
15 after pp	118.10 ± 2.44	124.80 ± 1.69	12.363	<0.001*
30 after pp	118.63 ± 2.57	124.77 ± 1.68	10.962	<0.001*
5 min after CO_2	114.33 ± 2.45	120.17 ± 2.05	9.987	<0.001*
5 min after extubation	109.90 ± 2.55	119.47 ± 2.27	15.345	<0.001*
Paired t-test				
3 min after intubation	0.005*	<0.001*		
Before PP	0.004*	<0.001*		
15 after PP	0.017*	<0.001*		
30 after PP	0.019*	<0.001*		
5 min after CO_2	<0.001*	0.006*		
5 min after ext.	<0.001*	0.019*		

Table 3 Changes in diastolic arterial pressure.

DBP	Groups			
	Group C ($n = 30$)	Group E ($n = 30$)	T-test	
	Mean ± SD	Mean ± SD	t	P-value
Baseline	79.37 ± 1.82	78.70 ± 1.51	1.552	0.126
3 MIN AFTER INT.	81.90 ± 0.92	84.03 ± 1.00	8.589	<0.001*
Before PP	75.17 ± 1.05	81.17 ± 0.91	23.579	<0.001*
15 min after PP	75.63 ± 1.88	84.13 ± 0.90	22.297	<0.001*
30 min after PP	74.73 ± 1.74	83.13 ± 0.94	23.273	<0.001*
5 min after CO_2	71.87 ± 1.74	81.13 ± 0.94	25.720	<0.001*
5 min after extubation	73.80 ± 1.61	79.13 ± 0.94	15.710	<0.001*
Paired t-test				
3 min after intubation	0.011*	<0.001*		
Before PP	<0.001*	<0.001*		
15 min. after PP	<0.001*	<0.001*		
30 min. PP	<0.001*	<0.001*		
5 min. after CO_2	<0.001*	<0.001*		
5 min. after extubation	<0.001*	0.010*		

Table 4 Changes in mean arterial pressure.

MBP	Groups			
	Group C ($n = 30$)	Group E ($n = 30$)	T-test	
	Mean ± SD	Mean ± SD	t	P-value
Baseline	92.30 ± 2.96	91.20 ± 2.78	1.484	0.143
3 min after intubation	93.13 ± 2.80	98.60 ± 1.35	11.385	<0.001*
Before PP	84.40 ± 2.75	94.07 ± 1.14	17.783	<0.001*
15 min. after PP	86.57 ± 2.81	93.30 ± 1.44	8.203	<0.001*
30 min. after PP	86.24 ± 2.82	93.04 ± 1.52	8.206	<0.001*
5 min. after CO_2	83.27 ± 2.73	87.72 ± 1.60	7.712	<0.001*
5 min. after extubation	82.73 ± 2.58	86.83 ± 1.53	7.478	<0.001*
Paired t-test				
3 min. after intubation	0.015*	<0.001*		
Before PP	<0.001*	<0.001*		
15 min. after PP	<0.001*	0.007*		
30 min. after PP	<0.001*	<0.001*		
5 min. after CO_2	<0.001*	<0.001*		
5 min. after extubation	<0.001*	<0.001*		

Degree of sedation according to Ramsay sedation score was assessed in patients 15 min after reaching PACU. The mean score in group C was significantly higher than the mean score in group E (Table 6).

4. Discussion

Our study confirms that clonidine and esmolol can successfully control hemodynamic changes in laparoscopic cholecystectomy; however clonidine has stronger effects on the hemodynamics with a sedative effect.

Laparoscopic cholecystectomy is considered a minimally invasive procedure. Hemodynamic changes with pneumoperitoneum were first recognized in 1947 [11]. Pneumoperitoneum using CO_2 for laparoscopic surgery causes a rapid and immediate increase in plasma catecholamines and vasopressin [12,13] possibly due to an increase in intraperitoneal pressure and stimulation of the peritoneum by CO_2. At intra-abdominal pressure of 15 mmHg, Joris et al. [4] found a 35% increase in mean arterial pressure, a 65% increase in systemic vascular resistance, and a 90% increase in pulmonary vascular resistance, while there was a 20% decrease in cardiac output. Plasma concentrations of renin also increase during laparoscopy [14]. The increase in catecholamines, renin and vasopressin induces a cardiovascular response characterized by abrupt elevations of arterial pressure, SVR and HR [15]. The increase in these hemodynamic values significantly increases the incidence of myocardial ischemia, infarction and other complications [16]. Various techniques such as gasless approach and many pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum. On the other hand, laryngoscopic stimulation of oropharyngeal structures may be an important factor in hemodynamic stress response associated with tracheal intubation [17]. Instrumentation of the pharynx and tracheal intubation

Table 5 Changes in heart rate.

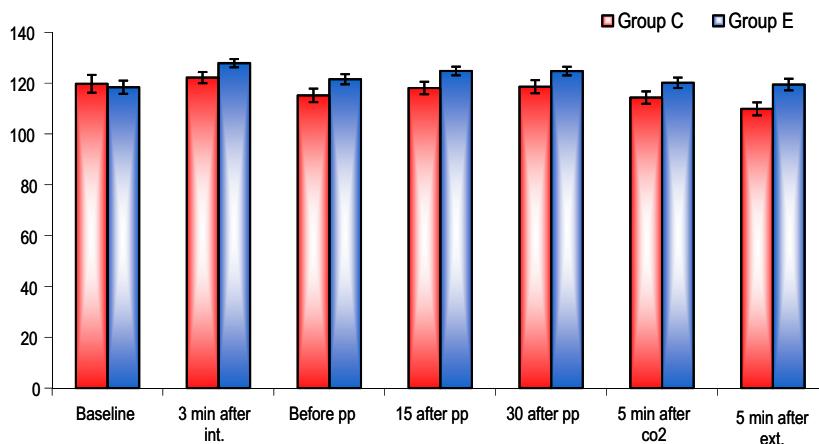| HR	Groups			
	Group C ($n = 30$)	Group E ($n = 30$)	T-test	
	Mean ± SD	Mean ± SD	t	P-value
Baseline	85.03 ± 2.27	84.20 ± 1.81	1.566	0.123
3 min. after intubation	84.03 ± 1.27	89.23 ± 1.25	15.962	<0.001*
Before PP	76.27 ± 2.29	81.93 ± 1.28	11.827	<0.001*
15 min. after PP	74.27 ± 2.16	78.93 ± 1.31	10.100	<0.001*
30 min. after pp	73.20 ± 2.11	79.33 ± 1.81	12.102	<0.001*
5 min. after CO_2	72.87 ± 2.08	81.40 ± 1.98	16.292	<0.001*
5 min. after extubation	69.93 ± 2.20	79.60 ± 1.81	18.597	<0.001*
Paired t-test				
3 min. after intubation	0.023*	<0.001*		
Before PP	<0.001*	<0.001*		
15 min. after pp	<0.001*	<0.001*		
30 min. after pp	<0.001*	<0.001*		
5 min. after CO_2	<0.001*	<0.001*		
5 min. after extubation	<0.001*	<0.001*		

Figure 1 Changes in systolic arterial blood pressure.
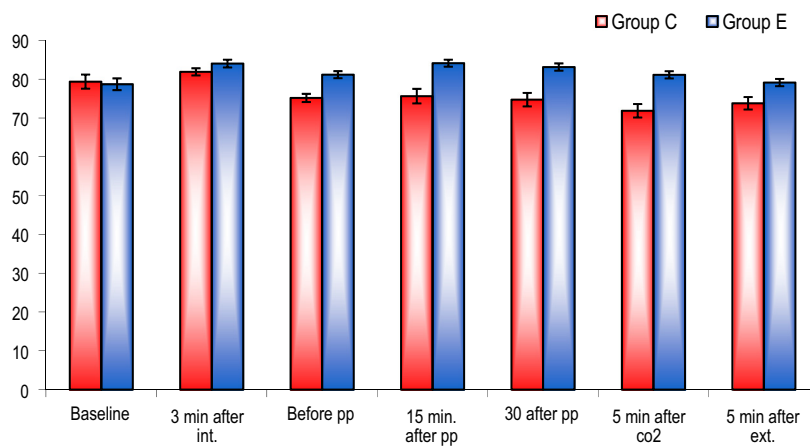

Figure 2 Changes in diastolic blood pressure.
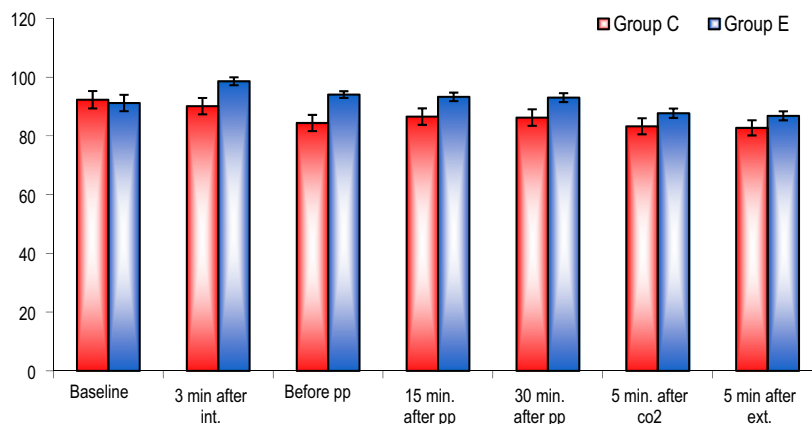
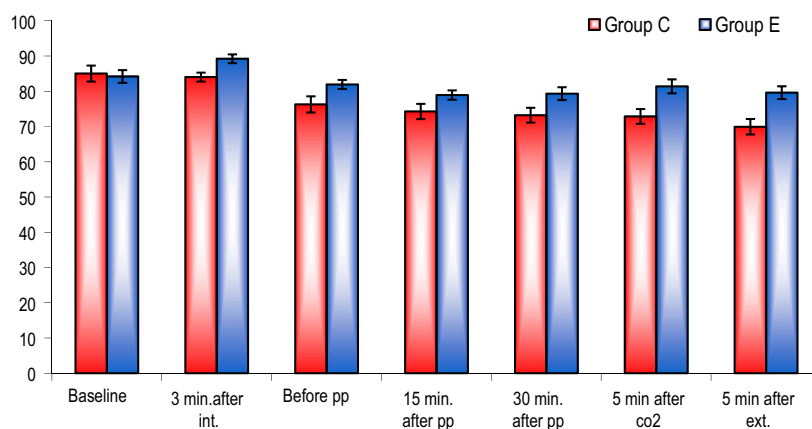**Figure 3**   Changes in mean arterial blood pressure.

Figure 4   Changes in heart rate.

Table 6   Sedation score comparison between the two groups.

Groups	Score		ANOVA	
	Range	Mean ± SD	f	P-value
Group C (n = 30)	1–4	2.53 ± 0.86	7.196	< 0.001[*]
Group E (n = 30)	0–2	1.13 ± 0.63		

PP: pneumoperitoneum.
  [*] Statistically significant.

may result in tachycardia, hypertension and increased catecholamine concentration that may evoke life threatening condition among susceptible individuals especially those with cardiovascular disease [18]. Also it may lead to occasional arrythmias, cough reflexes, increased intracranial pressure, and increased intraocular pressure. If no specific measures are taken to prevent the hemodynamic response, the HR can increase from 26% to 66% depending on the method of induction, and SBP can increase from 36% to 45% [19].

Our study compared between clonidine and esmolol because both of these drugs antagonize such hemodynamic changes during laparoscopy surgeries. Clonidine, a selective α-2 adrenergic agonist, has desirable actions such as anxiolysis, sedation, analgesia, antiemesis, and prevention of shivering. It is a potent hypotensive agent. Clonidine inhibits catecholamine and vasopressin-mediated increase in SVR caused by pneumoperitoneum [20]. Numerous studies using intravenous clonidine found effective prevention of hemodynamic derangements because of intubation and during laparoscopic cholecystectomy [21,22]. However, higher doses of clonidine resulted in significant bradycardia and hypotension [23]. Malek et al. [24] used 150 μg of clonidine as intravenous infusion while Sung et al. [25] and Yu et al. [26] used 150 μg of oral clonidine as premedication for maintenance of hemodynamic stability during pneumoperitoneum. Yu et al. even recommended its routine use as premedication in laparoscopic surgeries. Das et al. [27] also used 150 μg of oral clonidine 90 min prior to surgery to prevent hemodynamic response to pneumoperitoneum in laparoscopic cholecystectomy. Kalra et al. [28] used clonidine 1 μg/kg intravenously over a period of 15 min before pneumoperitoneum and clonidine group patients showed significantly better hemodynamic control than control group.

β-adrenergic receptor antagonists have also been used by various authors during surgery with the intention to attenuate the stress response of intubation and decrease the unwanted perioperative hemodynamic changes [29]. Esmolol is the selective β-adrenergic receptor blocker available and with its rapid

onset and extremely short duration of action, would appear to be an ideal drug for preventing acute increases in HR and SAP [30].

As an optimal intravenous (IV) esmolol dose for use during anesthesia induction (laryngoscopy and intubation) and emergence (extubation) has been previously determined in some studies to be 1.5 mg/kg, we used the same bolus dose in our study [31,32]. Moreover, many studies have demonstrated that beta adrenergic blockers that exert depressive effects on the central nervous system as esmolol also decreases the need for intraoperative anesthetic agents, leading to rapid recovery from anesthesia [31,33,34].

In this study, we compared between clonidine and esmolol in reduction of stress response and hemodynamic changes associated with laparoscopy. Both groups showed attenuation in SBP, DBP, MBP and HR increases in response to intubation with group C showing little increases compared to group E which was statistically significant. It was found that the SBP, DBP, and MBP values were lower with clonidine group compared to baseline values during pneumoperitoneum, release of CO_2 and after extubation than esmolol group and it was statistically significant. Just one patient in clonidine group suffered from significant hypotension but it was managed rapidly with fluids and ephedrine. Generally, the fluctuations in blood pressure during such operation were attenuated in both groups; therefore, we can safely conclude that clonidine and esmolol stabilize blood pressure during various phases of anesthesia and laparoscopy. After intubation, esmolol group showed little increase in mean heart rate compared to baseline value while in clonidine group, mean heart rate was lower than baseline value. However, the heart rate was lower in both groups during the surgery as compared to baseline values and it was statistically significant. Moreover, the mean heart rate was lower in group C compared with group E throughout the procedure and it was statistically significant. In spite of its more pronounced effect on heart rate, just 2 patients receiving clonidine suffered from significant bradycardia and required atropine injection. None of esmolol group suffered from bradycardia. Definitely, the heart rate lowering effect of both study drugs reduces the myocardial oxygen demand of the patient which can be very useful in patients suffering from coronary artery disease. The sedative effect of clonidine was obvious postoperatively compared with esmolol group but sedation was not that deep as patients were arousable either verbally or by touch.

5. Conclusion

In laparoscopic cholecystectomy the use of clonidine or esmolol will provide hemodynamic stability but with a postoperative sedative effect more with clonidine.

Source of funding

Conflict of interests

No conflict of interests.

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