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Research Article

Effect of esmolol infusion on myocardial oxygen consumption during extubation and quality of recovery in elderly patients undergoing general anesthesia: randomized, double blinded, clinical trial

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KEYWORDS

Esmolol;
Myocardial oxygen consumption;
Elderly;
Extubation;
Quality

Abstract *Background:* Upon recovery from anesthesia and during extubation, there will be mechanical stimulation of receptors in the respiratory tract that results in both respiratory and cardiovascular reflex responses. Heart rate plays a major determinant of myocardial oxygen consumption and cardiac workload, so decreasing the heart rate will increase the ischemic threshold and improve the cardiac performance.
Objective: To evaluate the effect of esmolol infusion on myocardial oxygen consumption during extubation and quality of recovery in elderly patients undergoing general anesthesia.
Methods: Hundred adult patients ASA I & II scheduled for elective open unilateral inguinal hernia were randomized, double-blindly into one of two parallel groups, esmolol group (E) ($n = 50$) and control group (C) ($n = 50$). In the esmolol group, 1 mg/kg esmolol was given as bolus over 30 s then followed by a continuous esmolol infusion of 100 μg/kg/min starting 10 min before end of surgery till 5 min after extubation. While patients in group C received normal saline bolus of the same volume followed by a continuous normal saline infusion of the same volume per hour as group E. Mean heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), rate pressure product (RPP), anesthesia time, recovery time, postoperative nausea & vomiting, number of doses of antiemetic agent and quality of extubation were recorded.
Results: The results showed that patients in the esmolol group had lower values of (RPP) after esmolol infusion with statistically significant difference when compared with patients in the control

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group using unpaired t-test ($P < 0.05$), this will decrease oxygen consumption in esmolol group. Also, there was statistically significant difference between both groups regarding values of HR (beat/min), SBP (mmHg), DBP (mmHg) and MBP (mmHg) starting 2 min after esmolol infusion and continued till 10 min after extubation using unpaired t-test ($p < 0.05$). As regards PONV, there was lower incidence in esmolol group when compared to control group using unpaired t-test with statistically significant difference ($P < 0.05$).

Conclusions: Esmolol is a safe, effective and well-tolerated drug that can be used in elderly patients undergoing general anesthesia to reduce the myocardial oxygen consumption and improve the quality of recovery.

1. Introduction

Upon recovery from anesthesia and during extubation, there will be mechanical stimulation of receptors which present in the larynx, trachea and bronchi. Stimulation of these receptors results in both respiratory and cardiovascular reflex responses [1]. Respiratory responses can be in the form of straining at aspiration, coughing, breath holding, or laryngospasm. However, the cardiovascular responses can be in the form of transient tachycardia, transient hypertension, arrhythmias, myocardial ischemia or infarction [2].

The hemodynamic changes can be explained by sympathetic overactivity during extubation which will lead to increased serum level of epinephrine and nor-epinephrine that results in tachycardia and hypertension. These hemodynamic changes can be well tolerated in healthy individuals but will have deleterious effects in patients with coronary artery disease, hypertension and cerebrovascular diseases [3].

In elderly patients, due to change in vascular elasticity, the hemodynamic changes associated with extubation are more likely to be exaggerated and may lead to increase oxygen consumption that results in myocardial ischemia and arrhythmia [4].

Myocardial ischemia occurs due to imbalance between myocardial oxygen supply and oxygen demand. Heart rate plays a major determinant of myocardial oxygen consumption and cardiac workload, so decreasing the heart rate will increase the ischemic threshold and improve the cardiac performance [5]. Myocardial ischemia is variable throughout the entire perioperative period, but it was found that postoperative myocardial ischemia occurs more often than preoperative (approximately 3:1) and intraoperative ischemia (approximately 5:1) [6].

Studies showed that postoperative myocardial ischemia can be used as a reliable predictor for in-hospital and long-term cardiac morbidity and mortality [7]. Because of myocardial oxygen consumption is difficult to be measured directly and the rate pressure product (RPP) index was found to correlate strongly with myocardial oxygen consumption, so RPP index can be used for estimation of myocardial oxygen consumption as it is easily measurable parameter [8].

Rate pressure product (RPP) is the product of systolic blood pressure (SBP) by heart rate (HR) and used for observation of myocardial oxygen consumption. It increases when myocardial oxygen requirements or consumption exceeds myocardial oxygen supply [9].

Many pharmacological agents have been used to control the hemodynamic changes during tracheal extubation with varying success rate such as local anesthetics, opioids, beta-blocking agents, and calcium channel blockers [10,11]. Among all these drugs β-adrenoceptor antagonists can be considered the only well-established prophylaxis against myocardial ischemia that demonstrates a reduction of patient morbidity and mortality [12]. Esmolol is an ultra-short acting cardioselective β1-receptor antagonist with half-life approximately 2 min and peak effect about 6–10 min. Because of these pharmacokinetic characteristics usually esmolol is used as a loading dose followed by continuous infusion [13]. It has been used for prevention and treatment of intra-operative and postoperative tachycardia and hypertension. Also, it has been reported to decrease plasma catecholamine levels and preventing hemodynamic changes during intubation, laryngoscopy and extubation [14].

The goal of this study was to evaluate the effect of esmolol infusion on myocardial oxygen consumption during extubation and quality of recovery in elderly patients undergoing general anesthesia.

2. Patients and methods

2.1. Study groups

After getting approval from the ethical committee of Dallah Hospital, Riyadh, Saudi Arabia, written informed consents were taken from all patients before entry into the study. This study was conducted on hundred (100) old adult male and female patients American Society of Anesthesiologist (ASA) physical status I–II, scheduled for elective open unilateral inguinal hernia repair during the period from May 2013 to April 2014, those patients were enrolled into one of two randomized, double-blind, controlled parallel group study using sequentially numbered, sealed, opaque envelopes.

Patients with uncontrolled systemic diseases (e.g. diabetes mellitus, asthma and chronic obstructive lung disease), significant organ dysfunctions (e.g. cardiac, respiratory, renal or liver disorders), morbid obese (BMI > 40), non-smokers, history of allergy to the drugs used, use of β-blockers or calcium channel blockers, chronic use of opioids or non-steroidal anti-inflammatory drugs, history of postoperative nausea & vomiting (PONV) or motion sickness were excluded from the study.

Patients were randomly divided into two groups, Esmolol group (group E $n = 50$) and Control group (group C $n = 50$). All patients were premedicated orally with bromazepam (3 mg) and ranitidine (150 mg) 1–2 h preoperatively. Ten minutes before end of surgery till five minutes after extubation, group E patients will receive unknown solution (A), while group C patients will receive unknown solution (B) in a double blind fashion. These solutions were prepared in the pharmacy, have the same volumes and the anesthetist was blinded to the grouping design.

In group E, patients received esmolol hydrochloride (*Brevibloc premixed, 10 mg/ml, Baxter Healthcare Corporation, USA*) 1 mg/kg as bolus dose over 30 s followed by a continuous esmolol infusion of 100 μg/kg/min starting 10 min before end of surgery till 5 min after extubation. While patients in group C received normal saline bolus of the same volume followed by a continuous normal saline infusion of the same volume per hour as group E.

2.1.1. Anesthetic technique

On arrival of the patient to the operating theater, all standard monitors were applied including heart rate (HR), electrocardiogram (ECG), oxygen saturation (Spo2), end-tidal CO2, arterial blood pressure (systolic (SBP), diastolic (DBP) & mean (MAP)) and temperature. In addition to these monitors, both neuromuscular monitoring, train of four (TOF) and bipolar BIS electrodes (BIS QUATRO-BX13366, Aspect Medical Systems, Inc.USA) were applied to the patient. After induction of anesthesia, arterial catheter was inserted in the radial artery for continuous blood pressure monitoring and frequent blood gas analysis. Initial or baseline readings of all these monitors were taken and recorded before starting any drug infusion (base line) in the pre-anesthetic period, then during intraoperative period also.

Anesthesia was induced by intravenous remifentanil (1 μg/kg) over 30–60 s, followed by propofol (1–2 mg/kg). Intubation was performed using rocuronium bromide in a dose of (0.6 mg/kg). Maintenance of anesthesia was carried by continuous infusion of remifentanil (0.25 μg/kg/min), sevoflurane 1–2% MAC and 50% air in oxygen. Anesthesia was titrated to keep the ‘BIS’ value within the range (50–60). Muscle relaxation was monitored by ‘TOF’ for every ten minutes, rocuronium infusion from 0.3 to 0.6 mg/kg/hr was given and adjusted to maintain 1–2 responses to ‘TOF’ stimulation. Lungs were mechanically ventilated to maintain normocapnia (Etco2 35–40 mmHg). All surgical procedures were done by the same surgeon who was blind about the study.

All vital signs were recorded before induction of anesthesia (preoperative), before esmolol infusion (base line for the study), 2 min after starting infusion, before extubation, then 1, 3, 5, and 10 min after extubation. All patients were anesthetized by one anesthetist who was not involved in the study and was instructed to follow the study design. Lactated Ringer’s solution was set at a rate of 6 ml/kg/hr as a baseline infusion in both groups. Additional solutions were infused if required. Neither anti-inflammatory drugs nor local anesthetic infiltration of the surgical wounds were used in both groups.

The following medications were used when needed, atropine sulfate 0.5 mg was used for bradycardia (HR < 50 beats/min), ephedrine 5 mg was used for hypotension not responding to IV fluids (SBP < 30% of the base line for more than 60 s). Increase in SBP more than 30% of the base line for more than 60 s or HR more than 130 beats/min for longer than 60 s was managed by increasing the anesthetic depth by increasing MAC sevoflurane by 1%.

At the end of surgery, all anesthetic agents were discontinued and the patients were ventilated with 100% oxygen. The residual effect of rocuronium was reversed with neostigmine in a dose of 40 μg/kg and glycopyrolate 20 μg/kg. Then the patients were extubated after regaining their spontaneous breathing and transferred to the postanesthesia care unit for routine follow up. Every patient was observed continuously during and after termination of anesthesia. The quality of extubation was assessed using a 5-point rating scale, where 1: no cough and normal breathing, 2: mild cough, 3: moderate cough, 4: severe cough and difficulty in breathing, and 5: laryngospasm with severe cough. PONV was also assessed & graded on a 5-point scale; 0: no nausea, 1: mild nausea, 2: moderate nausea, 3: severe nausea and 4: retching or vomiting. Patients with PONV received 8 mg ondansetron hydrochloride IV & the total dose of antiemetic was calculated during the first 24 h after surgery.

2.1.2. Data for assessments

- Mean heart rate (HR) (beats/min).
- Systolic blood pressure (SBP) (mmHg).
- Diastolic blood pressure (DBP) (mmHg).
- Mean arterial blood pressure (MAP) (mmHg).
- Rate pressure product (RPP) (beats/min mmHg).
- Duration of anesthesia (in minutes); from the time of induction to withdrawal of all anesthetics.
- Recovery time (in minutes); from withdrawal of all anesthetics to extubation.
- PONV.
- Number of doses of antiemetic agent.
- Quality of extubation.

2.1.3. Statistical analysis

Sample size was calculated guided by the following data power of the test 80% with beta error 20% and alpha error accepted to be 5%. Confidence level was 95%, success rate of the technique was used in special formula for calculation to be 100 totally classified 1:1. Analysis of data was done by IBM computer using SPSS (statistical package for social science version 12) as follows; description of quantitative variables as mean, SD and range then, description of qualitative variables as number and percentage. Chi-square test was used to compare qualitative variables between both groups. Unpaired *t*-test was used to compare quantitative variables in parametric data (SD < 50% mean) and paired *t*-test was used to compare quantitative variable in the same group. P value > 0.05 is considered insignificant, P value < 0.05 is significant, while P value < 0.001 is highly significant (see Fig. 1).

3. Results

3.1. Demographic & operative data of patients

Analysis of the results showed that there was no significant difference in demographic and operative data of the patients between the two groups (Table 1).

3.2. Hemodynamics

The results of current study showed that there were no difference between esmolol and control groups regarding values of mean heart rate (beat/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and mean blood pressure

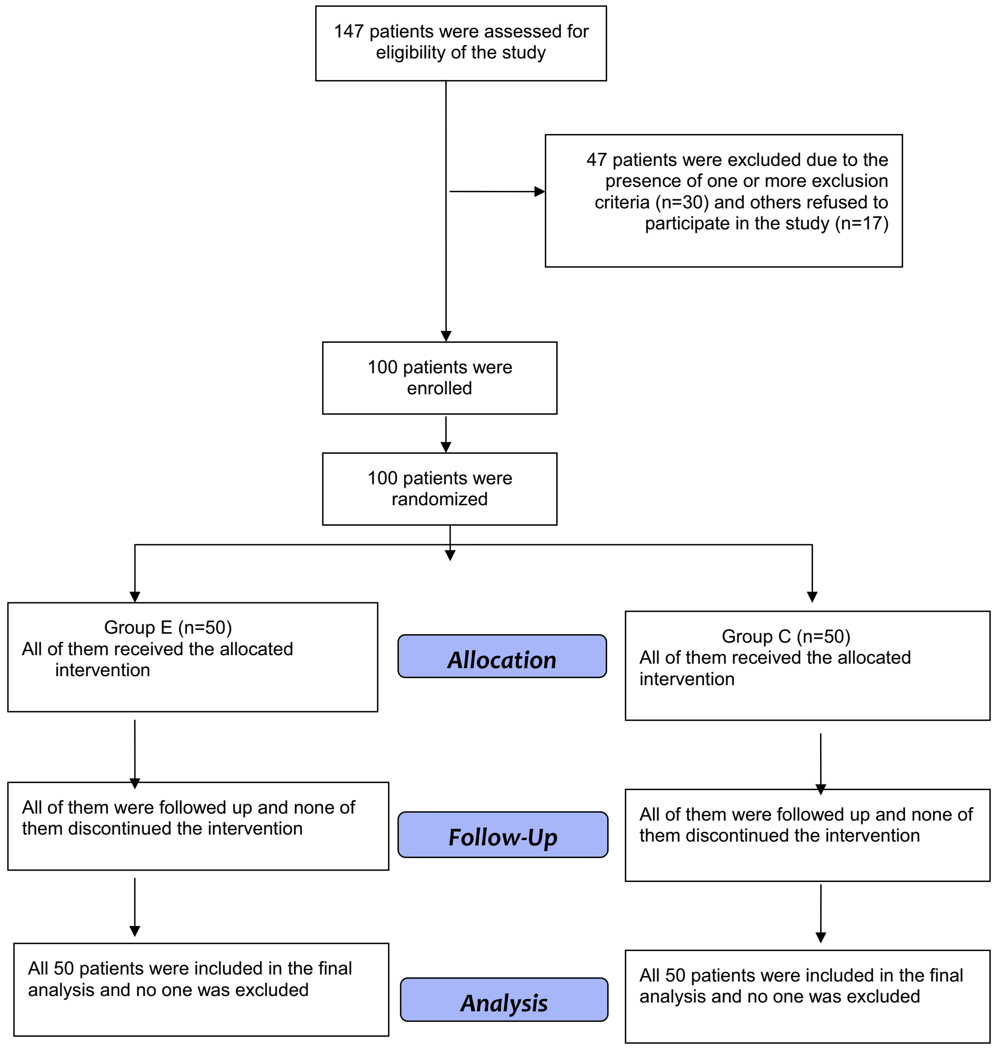

Figure 1 Flow diagram of participants in the current study.

Table 1 Demographic and operative data (mean ± SD).

	Esmolol group (n = 50)	Control group (n = 50)	t	P
Age (yr) range	55–68(60 ± 3)	57–66(62 ± 4)	0.8	0.44 NS
Sex			Fisher exact	0.37
Male	44	43		NS
Female	6	7		
Weight (kg)	68–88(82.6 ± 6)	67–98(85 ± 10)	0.9	0.30 NS
Height (cm)	160–179(165 ± 10)	158–178(166 ± 8)	1.1	0.27 NS
ASA (I/II)	38/12	36/14	Fisher	0.56 NS
Duration of surgery (min)	48–70(60 ± 5)	50–72(61.6 ± 8)	1.5	0.20 NS
Duration of anesthesia (min)	55–75(65.8 ± 7)	54–76(63 ± 8)	1.1	0.23 NS
Recovery time (min)	3–7(5.6 ± 1.6)	6–12(9 ± 2.5)	1.4	0.19 NS

(mmHg) preoperatively till 2 min after esmolol infusion ($P > 0.05$). However, there was statistically significant difference between both groups regarding the same parameters starting 2 min after esmolol infusion and continued till 10 min after extubation using unpaired t-test ($p < 0.05$) (Figs. 2–5).

On the other hand there was statistically significant difference among the patients in the esmolol group regarding values of mean heart rate (beat/min), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) before and after esmolol infusion ($P < 0.05$) using paired t-test. Meanwhile, there was no difference regarding values of mean blood pressure

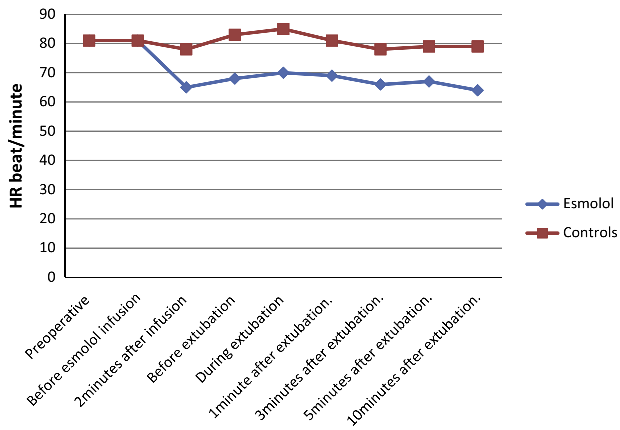

Figure 2 Mean heart rate values in both groups (beat/min).

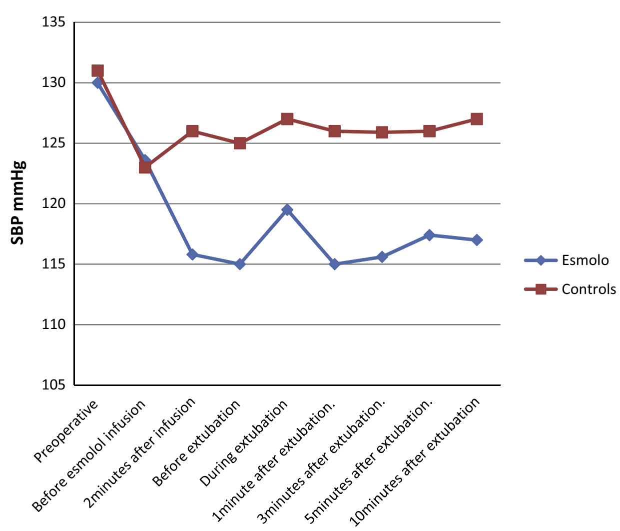

Figure 3 Systolic blood pressure values in both groups (mmHg).

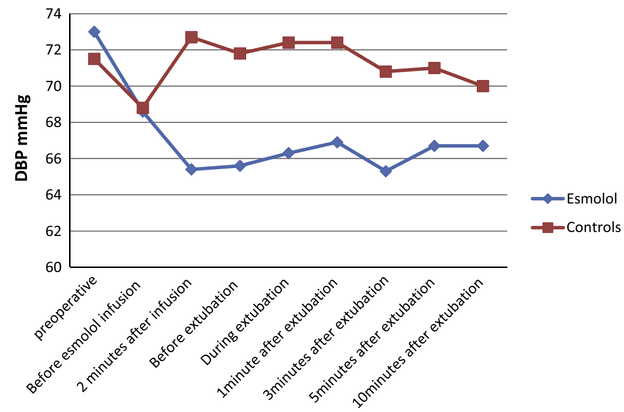

Figure 4 Diastolic blood pressure values in both groups (mmHg).

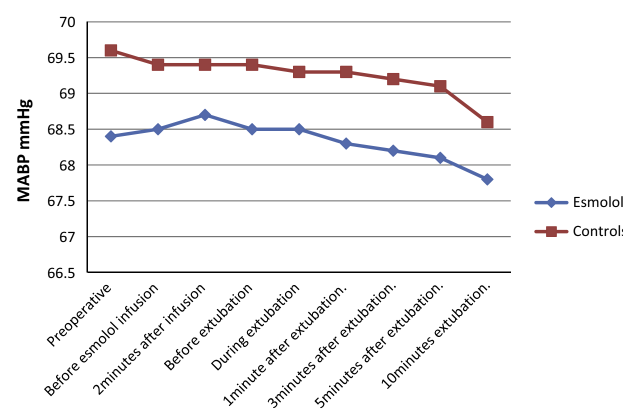

Figure 5 Mean blood pressure values in both groups (mmHg).

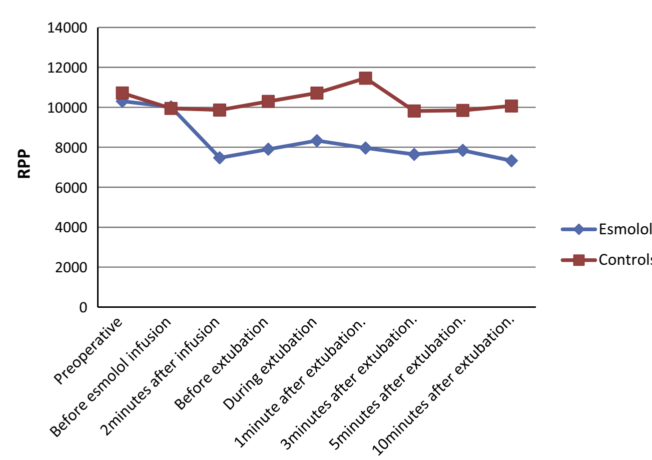

Figure 6 Rate pressure product (RPP) values in both groups (beat/min mmHg).

(mmHg) among those patients in that group before and after esmolol infusion ($p > 0.05$) (Figs. 2–5).

3.3. Rate pressure product (RPP) and oxygen consumption

The results of this study demonstrated that patients in the esmolol group had lower values of (RPP) after esmolol infusion and continued up to 10 min after extubation with statistically significant difference when compared with patients in the control group using unpaired *t*-test ($P < 0.05$). Consequently, the myocardial oxygen consumption and myocardial ischemia will be less among those patients. On the other hand, there was statistically significant difference among patients in esmolol group regarding RPP before and after esmolol infusion using paired *t*-test ($P < 0.05$) (Fig. 6).

3.4. Quality of recovery

3.4.1. Postoperative nausea & vomiting (PONV)

The results of our study showed that there was lower incidence of PONV among patients in esmolol group when compared to patients in the control group using unpaired *t*-test with statistically significant difference ($P < 0.05$). Only 3 patients in esmolol group (6%) who had severe nausea compared to 20 patents (40%) in the control group (Table 2). Regarding the total number of doses of antiemetic agent, it was found that 26 (52%) patients in the control group received 2 or more doses compared to 11 (22%) patients in the esmolol group with

Table 2 Postoperative nausea & vomiting (number &%).

Grade	Esmolol group ($n = 50$)	Control group ($n = 50$)	X^2	P
0 (no nausea)	21(42%)	0 (0%)	6.8	0.02 S
1 (mild nausea)	18 (36%)	9 (18%)		
2 (moderate nausea)	8 (16%)	15 (30%)		
3 (severe nausea)	3 (6%)	20 (40%)		
4 (vomiting)	0 (0%)	6 (12%)		

Table 4 Extubation quality scale (number &%).

Grade	Esmolol group ($n = 50$)	Control group ($n = 50$)	X^2	P
1	23 (46%)	0 (0%)	7.4	0.002 S
2	18 (36%)	8 (16%)		
3	6 (12%)	17 (34%)		
4	3(6%)	19 (38%)		
5	0 (0%)	6 (12%)		

statistically significant difference ($P < 0.05$) using unpaired *t*-test (Table 3).

3.4.2. Extubation quality

The results of current study documented that the majority of patients in the esmolol group (41 patients = 82%) had no or mild cough and only 9 (18%) patients had moderate to severe cough compared to 36 (72%) patients in the control group had moderate to severe cough while only 9 (18%) patients had mild or no cough with statistically significant difference ($P < 0.05$) using unpaired *t*-test (Table 4). There are 6 (12%) in the control group had severe cough with laryngospasm while no patients in the study group had.

4. Discussion

4.1. Hemodynamic responses and oxygen consumption;

Withdrawal of anesthetic drugs during recovery from general anesthesia is usually associated with marked elevations in both heart rate and arterial blood pressure before and during extubation due to release of catecholamine in the circulation [15]. As result of these hemodynamic changes together with some degree of cardiovascular disease in old patients, myocardial ischemia due to increased myocardial oxygen consumption can occur [16].

Rate-pressure product (RPP) index that results from multiplying systolic blood pressure (SBP) by heart rate (HR) can be used as a relevant parameter in evaluating the myocardial oxygen consumption and ventricular function, the higher the RPP index the higher the possibility of myocardial ischemia [9]. Many prophylactic pharmacological measures have been used to control the hemodynamic changes that happen during recovery from anesthesia and extubation [17]. Among these medications, opiate analgesics, calcium channel blockers, nitrates, lidocaine, dexmedetomidine & esmolol [18–20]. The pharmacokinetics of ultra-short acting, cardioselective, beta blocker esmolol make it the drug of choice in situations with high catecholamine levels such as emergence from general anesthesia and during tracheal extubation [21].

The present study shows that esmolol hydrochloride reduced HR, SBP, MAP, and RPP from starting the infusion till after extubation. Thus, the cardiac work load will reduce and consequently the myocardial oxygen consumption & perioperative myocardial ischemia. This result was in agreement with results of other studies. In 2013, Alkaya et al. [1] reported that esmolol infusion in a dose of 2 mg/kg 5 min before extubation can prevent tachycardia and hypertension associated with extubation in patients undergoing elective craniotomy.

In a meta-analysis of 32 randomized trials including 1765 patients Landoni et al. [22] studied if esmolol reduces the perioperative ischemia in noncardiac surgery or not. They found that use of esmolol was accompanied by great reduction in myocardial ischemic episodes (5/283 [1.76%]) in the esmolol group compared to (16/265 [6.03%]) in the control group with $p = 0.003$. In addition, the use of esmolol was associated with lower incidence of hypotension (17/384 [4.42%] v 38/439 [8.65%]) with $p = 0.17$ and bradycardia (25/342 [7.30] v 17/406 [4.18%]) with $p = 0.42$ when compared to control group. Finally, they concluded that esmolol can reduce myocardial ischemia in noncardiac surgery without causing episodes of hypotension or bradycardia.

In a comparative study between different doses of esmolol on the hemodynamic response due to extubation, Wang et al. [23] found that 1.5 mg/kg and 2.0 mg/kg doses of esmolol were effective in controlling both the heart rate and blood pressure during extubation. Also, the result of this study was in accordance with another study that was done by Singh et al. [24] who studied the effect of esmolol on the cardiovascular response during laryngoscopy & intubation and concluded that esmolol in a dose of 2 mg/kg is effective in attenuating the hemodynamic responses to laryngoscopy and intubation without any complications such as bradycardia or hypotension. In a study done by Dyson et al. [25] it was demonstrated that esmolol in a dose of either 1.5 mg/kg or 2.0 mg/kg was effective in controlling the tachycardia and hypertension during extubation, but esmolol 1 mg/kg was ineffective.

On the other hand, this study come in contrast with another study reported that both esmolol and lidocaine can attenuate the hemodynamic responses to intubation but not during extubation [26].

4.2. Quality of recovery

4.2.1. Postoperative nausea and vomiting (PONV)

The Postoperative nausea and vomiting (PONV) is considered as one of the most commonly reported complications of gen-

Table 3 Total number of doses of antiemetic agent (ondansetron HCl) (number &%).

Number of doses	None	1	2	⩾3	X2	P
Esmolol group ($n = 50$)	21(42%)	18 (36%)	8 (16%)	3 (6%)	5.90	0.03 S
Control group ($n = 50$)	0 (0%)	24 (48%)	20 (40%)	6 (12%)		

eral anesthesia. It represents 10% in patients without any risk factor but may reach up to 61–79% in the presence of 3 or 4 risk factors respectively [27]. Inhalational general anesthetics and nitrous oxide have greater risk for PONV (59%) than intravenous general anesthetics (28%). The presence of PONV will increase the patient's morbidity, length of hospital stay and the overall costs [28].

The current study shows that the patients in esmolol group have less incidence of PONV compared to the patients in the control group and also, they received less total number of anti-emetic agent than the control group. These results are in agreement with another study done by Coloma et al. [29] who concluded that the use of esmolol in outpatient gynecologic procedures done under desflurane & remifentanil anesthesia was associated with less incidence of PONV. Also, in 2007 Oztruk et al. [30] did another study on 40 patients undergoing laparoscopic cholecystectomy and reported that the combination of esmolol & alfentanil was associated with less rate of PONV.

Although there is no definite mechanism for the antiemetic effect of esmolol, but it can be explained partly by the opioids sparing effect & the prevention of hemodynamic instability occurring during stress periods of anesthesia and surgery.

4.2.2. Quality of extubation

The results of this study demonstrate that use of esmolol was accompanied by smooth recovery and good quality of extubation with low incidence of cough and laryngospasm among these patients. Our results are in accordance with the results of Alkaya et al. [1] who studied the effect of esmolol on hemodynamic responses to tracheal extubation after craniotomy surgeries and reported that the majority of patients in the esmolol group had better extubation quality score when compared to the patients in the control group.

4.2.3. In conclusion

From the previously mentioned data, we can conclude that esmolol is a safe, effective and well-tolerated drug that can be used in elderly patients undergoing general anesthesia to reduce the myocardial oxygen consumption and improve the quality of recovery.

Conflict of interest

No conflict of interest.

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