ARAŞTIRMA/RESEARCH

Effect of intraoperative esmolol infusion on postoperative stress response in a group of laparoscopic cholecystectomy patients

Bir grup laparoskopik kolesistektomi hastasında intraoperatif esmolol infüzyonunun postoperatif stres yanıt üzerine etkisi

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Abstract

Purpose: We aimed to analyze effects of esmolol on intraoperative anesthetic-postoperative analgesic requirements, postoperative cortisol and prolactin levels.

Material and Methods: Sixty patients have been included. Study groups were as follows; 1: Esmolol infusion was added to propofol and remifentanil, 2: Only propofol and remifentanil, 3: Esmolol infusion was added to desflurane and remifentanil, 4: Only desflurane and remifentanil was used. Preoperative and postoperative cortisol and prolactin levels were measured.

Results: Analgesic requirements were significantly lower in group 1 and was lower in group 3 compared to group 4. Heart rates were significantly lower in esmolol groups (group 1 and 3) compared to their controls. Prolactin levels significantly increased postoperatively in all groups compared to preoperative levels. We observed a significant decrease in cortisol levels postoperatively in group 1 compared to preoperative levels.

Conclusion: Using adjuvant esmolol during anesthetic – analgesic requirements without causing any hemodynamic instability, and suppresses postoperative cortisol response but does not have any significant effect on postoperative prolactin response.

Key words: Esmolol, postoperative stress response, cortisol, prolactin

INTRODUCTION

Laparoscopic cholecystectomy is a daily routine procedure with low cost and high patient satisfaction by developments in surgical and anesthetic techniques. Intra and postoperative hemodynamic stability and efficient analgesia is important to decrease incidence of postoperative complications¹₂. In these patients hemodynamic stress responses like hypertension and tachycardia might develop as a reflex to endotracheal intubation or surgical intervention itself.
Insufflation of CO₂ into peritoneal cavity might also trigger this response. Sympathoadrenergic reflex causes some metabolic and neuroendocrine reactions. Increased catecholamine secretion results in increased blood pressure and tachycardia. These might increase myocardial O₂ requirements but also decrease coronary blood flow and diastolic filling duration. This situation could be well tolerated in otherwise healthy patients however could have devastating results in elder patients with ischemic heart disease or comorbidities like diabetes mellitus.

Surgical stress response is characterized by increased serum levels of catecholamines, cortisol, antidiuretic hormone (ADH), growth hormone (GH), glucose, lactate and their metabolites. This increase is closely related with the severity of surgical intervention and is usually higher in abdominal surgeries. Plasma concentrations of stress hormones might also increase secondary to side effects of some anesthetic agents.

Different techniques or anesthetic agents could be used to decrease hemodynamic response and related postoperative complications. Increasing volatile anesthetic concentrations and/or opioid usage are some methods that could be preferred. Sympatholytic agents decrease hemodynamic response and so requirement for opioids. These agents are alternatives for opioids and also might decrease requirements for intravenous or inhalation anesthetics. In this study we aimed to analyze effects of esmolol, a cardioselective beta-1 (β₁) adrenergic receptor antagonist, on intraoperative anesthetic- and postoperative analgesic requirements, postoperative cortisol and prolactin levels.

**MATERIAL AND METHODS**

Study was designed as a prospective study and was approved by local ethical committee (Ethical Committee of the Kecioren Training and Research Hospital, Date: 09.01.2013/ Number: 174).

Sixty patients aged between 18-60 years who underwent laparoscopic cholecystectomy have been included. The patients were provided with details of the study to which they gave a written informed consent. Exclusion criteria were as follows; previously known cardiovascular disease, severe hemodynamical instability during operation [mean blood pressure (MBP) < 70 mmHg], chronic opioid usage, asthma, being obese or underweighted (body mass index > 30 or < 18.5), diabetes mellitus, using β blockers or calcium channel blockers.

No premedications were used before operation. Electrocardiographic (ECG), invasive intraarterial blood pressures, MBP, peripheral oxygen saturations (SpO₂) ve bispectral index (BIS) monitorizations were performed and recorded as study data. Propofol 2.5 mg/kg, remifentanil 1µg/kg and vecuronium 0.1 mg/kg were used for induction in all patients. %50 O₂ and fresh air mixture was used during mechanical ventilation. End-tidal CO₂ (ETCO₂) levels were aimed to be between 35-45 mmHg and fresh gas flow rate was 3 lt/min in all patients.

Study groups were as follows;

**Group 1:** After induction, 5 minute esmolol infusion (total dose 1 mg/kg) was used. Peroperative esmolol dose was planned as 10 µg/kg/min. Maintenance anesthetics were 75-85 µg/kg/min propofol and 0.2 µg/kg/min remifentanil.

**Group 2:** Maintenance anesthetics were 75-85 µg/kg/min propofol and 0.2 µg/kg/min remifentanil. No esmolol infusion was used.

**Group 3:** After induction, 5 minute esmolol infusion (total dose 1 mg/kg) was used. Peroperative esmolol dose was planned as 10 µg/kg/min. Maintenance anesthetics were %4-8 desflurane and 0.2 µg/kg/min remifentanil.

**Group 4:** Maintenance anesthetics were %4-8 desflurane and 0.2 µ/kg/min remifentanil. No esmolol infusion was used.

Group 2 was designed as control for group 1 and group 4 was designed as control for group 3. Adjustments in esmolol and other anesthetic drug dosages were done according to MBP and heart rates of all individual patient as follows. Propofol and desflurane concentrations were changed continuously during operation by aiming BIS values between 40-60.

Intravenous atropine and ephedrine were planned to be used in case of any intraoperative bradycardia (40 pulse/min) or hypotension (MBP < 70 mmHg). In case of a decrease in heart rates and MBP near to above mentioned critical levels we first decreased remifentanil infusion rates and then decreased esmolol infusion rates. Total requirements of
propofol, remifentanil, esmolol and desfluran were calculated and recorded for each patient.

All patients were followed up in postoperative critical care (PACU) unit for at least 30 minutes after surgery. Postoperative ECG, MBP, heart rates, peripheral SpO2 monitorizations were performed and recorded as study data. 10 mg metoclopramide iv was applied to all patients in PACU. All patients were discharged from PACU to standart care clinics after they had an Aldrete score < 9 and they have been followed up for another 24 hours for PNV and analgesic requirements.

Preoperative cortisol and prolactin levels were measured from a venous blood sample which was drawn just before initiation of anesthesia procedure and intubation. Postoperative cortisol and prolactin levels were measured from a venous blood sample which was drawn after 24 hours of leaving PACU. Cortisol and prolactin levels were studied with a Beckman Coulter, UniCel Dxl 800 Access Immunoassay System (CA, USA).

**Statistical analysis**

Statistical Package for Social Sciences (SPSS for Windows, Chicago, IL, USA) version of 14.0 was used for data analysis. Data were submitted to a frequency distribution analysis by Kolmogorov-Smirnov's test. Values displaying normal distribution were expressed as the mean ± SD and values with skew distribution were expressed as median (interquartile range).

Differences between numeric variables were tested with One-Way ANOVA or Kruskal-Wallis tests where appropriate. Tukey test was used for post-hoc analyses. Paired samples t-test or Wilcoxon signed-rank test was used to compare two related samples. Categorical data were compared by chi-square or Fisher's tests. The value of confidence interval was accepted as 95% and statistical significance was accepted as: "p<0.05".

**RESULTS**

Sixty laparoscopic cholecystectomy patients (45 female, age: 47.8 ± 12.1 years) were included. Study groups were statistically similar in means of demographic (age and gender distribution) characteristics (Table 1). Surgery and anesthesia durations were also similar however there was a tendency for increased surgery (p: 0.054) and anesthesia durations (p: 0.097) in group 1 and group 2 compared to groups 3 and 4 (Table 1). These durations were similar when esmolol groups were compared with only their controls (group 1 vs 2 and group 3 vs 4).

Mean BIS values were similar between groups and were between 40-60 (p: 0.270). When compared in means of hemodynamical parameters heart rates were significantly lower in esmolol groups (group 1 and 3) compared to their controls (p: 0.001) however MBP values were similar in all groups (p: 0.594). Heart rates and MBP values in PACU were similar between groups (p: 0.327, 0.094 respectively). Comparison of esmolol groups with controls in means of anesthetic requirements revealed that there is a significant decrease in desflurane, propofol and remifentanil requirements (p: 0.024, 0.03, 0.026 respectively).

In means of preoperative prolactin and cortisol levels study groups were similar. Prolactin levels significantly increased postoperatively in all groups compared to preoperative levels (p: 0.005 – 0.001, Table-1 and Figure-1). However there was no significant difference between study groups in means of postoperative prolactin levels when compared to each other (p: 0.478).

We also observed a significant decrease in cortisol levels postoperatively in group 1 compared to preoperative levels (p: 0.037, Table-1, Figure-2). There was also a decrease in postoperative cortisol levels in group 3 but it did not have statistical significance (p: 0.1). In groups 2 and 4 there was a significant increase in postoperative cortisol levels compared to initial values (p: 0.003, 0.008 respectively). When we compared postoperative cortisol values of study groups with each other we observed that control groups (groups 2 and 4) had significantly higher cortisol levels compared to groups 1 and 3 (p: 0.034, Table-1, Figure-2).

**DISCUSSION**

Anesthesia induction, laryngoscopy and tracheal intubation might induce a stress response that increase incidence of some intraoperative or postoperative complications like hemodynamic instability, myocardial ischemia and infarction. Epipharyngeal and laryngopharyngeal irritation induces cervical sympathetic system activation and catecholamine secretion. Increased serum...
catecholamine levels cause some hemodynamic changes like hypertension and tachycardia. These hemodynamic changes not only increase myocardial O₂ requirements but also increase intracranial and intraocular pressures and might cause specific risks in susceptible patients.

In laparoscopic surgeries pneumoperitonium is an additional risk factor. Insufflation of CO₂ causes a rapid increase in arterial and central venous blood pressures, heart rates and systolic vascular resistance. These factors also contribute to increased myocardial O₂ requirements and trigger cardiovascular complications in patients with decreased cardiac reserve. Vasopressor response is a result of combined activation of sympathetic, hypothalamic and renin angiotensin aldosterone systems. Functional magnetic resonance imaging studies reported that there is a hippocampal activation during emotional distress, fear or anxiety. This hippocampal activation is thought to be secondary to a stress related factor like norepinephrine that increases hippocampal neuronal activity. N-metil D-aspartat (NMDA) and adrenergic receptors at hippocampus also play role in nociception. Blocking these receptors decrease amplitude of patients' perception of pain.

Table 1. Comparison of study groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n:12)</th>
<th>Group 2 (n: 15)</th>
<th>Group 3 (n: 21)</th>
<th>Group 4 (n: 12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>9/3</td>
<td>12/3</td>
<td>15/6</td>
<td>8/4</td>
<td>0.724</td>
</tr>
<tr>
<td>Gender (years)</td>
<td>44.3 ± 13.2</td>
<td>45.3 ± 14.2</td>
<td>51.7 ± 9.3</td>
<td>48.8 ± 11.9</td>
<td>0.318</td>
</tr>
<tr>
<td>Surgery duration (min)</td>
<td>79.1 ± 23.9</td>
<td>82.6 ± 31.3</td>
<td>62.2 ± 24.1</td>
<td>55.5 ± 23.5</td>
<td>0.054</td>
</tr>
<tr>
<td>Anesthesia duration (min)</td>
<td>92.1 ± 25.6</td>
<td>91.1 ± 35.7</td>
<td>77.7 ± 22.9</td>
<td>68.1 ± 24.8</td>
<td>0.097</td>
</tr>
<tr>
<td>Preoperative prolactin levels</td>
<td>8.9 (6.3)</td>
<td>7.7 (8.6)</td>
<td>6.2 (6.8)</td>
<td>9.6 (4.7)</td>
<td>0.484</td>
</tr>
<tr>
<td>Preoperative cortisol levels</td>
<td>14.8 (14.4)</td>
<td>11.4 (10.5)</td>
<td>13.1 (12.8)</td>
<td>13.1 (6.2)</td>
<td>0.79</td>
</tr>
<tr>
<td>Postoperative prolactin levels (ng/mL)</td>
<td>96.6 (38.4)</td>
<td>119.1 (112.5)</td>
<td>83.6 (101.6)</td>
<td>76.1 (91.4)</td>
<td>0.478, 0.005*, 0.001**</td>
</tr>
<tr>
<td>Postoperative cortisol levels (ng/mL)</td>
<td>10.8 (8.2)</td>
<td>15.3 (20.6)</td>
<td>10.3 (6.2)</td>
<td>18.8 (12.2)</td>
<td>0.034, 0.037**, 0.003**, 0.008***</td>
</tr>
<tr>
<td>Intraoperative heart rate (pulse/min)</td>
<td>66.4 ± 9.1</td>
<td>77.4 ± 7.5</td>
<td>69.3 ± 6.4</td>
<td>72.8 ± 6.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Intraoperative mean blood pressure (mmHg)</td>
<td>91 ± 15.7</td>
<td>92.1 ± 11.7</td>
<td>91.6± 8.3</td>
<td>86.6 ± 10.8</td>
<td>0.594</td>
</tr>
<tr>
<td>Heart rate in PACU (pulse/min)</td>
<td>63.6 ± 11.9</td>
<td>72.9 ± 12.4</td>
<td>67.4 ± 12.1</td>
<td>65.7 ± 15.6</td>
<td>0.327</td>
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<tr>
<td>Mean blood pressure in PACU (mmHg)</td>
<td>79.7 ± 15.1</td>
<td>89.1 ± 16.3</td>
<td>80.9 ± 13</td>
<td>76.8 ± 9.5</td>
<td>0.094</td>
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<tr>
<td>Mean BIS value</td>
<td>51.9 ± 20.2</td>
<td>51.7 ± 12.6</td>
<td>46.7 ± 9.4</td>
<td>43.4 ± 8.5</td>
<td>0.270</td>
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<tr>
<td>Propofol requirements (mL)</td>
<td>328.4 ± 173.8</td>
<td>530.1 ± 244.1</td>
<td>-</td>
<td>-</td>
<td>0.024*</td>
</tr>
<tr>
<td>Desflurane requirements (mL)</td>
<td>-</td>
<td>-</td>
<td>31.2 ± 12.3</td>
<td>43.6 ± 18.9</td>
<td>0.03**</td>
</tr>
<tr>
<td>Remifentanil requirements (mL)</td>
<td>174.6 ± 100.8</td>
<td>269.2 ± 105.2</td>
<td>132.9 ± 146.0</td>
<td>562.4 ± 152.4</td>
<td>0.026*, 0.0001**</td>
</tr>
</tbody>
</table>

*; p level for pre-postoperative prolactin level comparisons for groups 1 and 4; **; p level for pre-postoperative prolactin level comparisons for groups 2 and 3; ***; p level for pre-postoperative cortisol level comparisons for group 1; †; p level for pre-postoperative cortisol level comparisons for group 3; ‡; p level for pre-postoperative cortisol level comparisons for group 4
Prolactin levels significantly increased postoperatively in all groups compared to preoperative levels (groups 1 and 4; p: 0.005, groups 2 and 3; p: 0.001). However there was no significant difference between study groups in means of postoperative prolactin levels when compared to each other (p: 0.478).

There was a significant decrease in cortisol levels postoperatively in group 1 compared to preoperative levels (p: 0.037). Decrease in in group 3 did not have statistical significance (p: 0.1). In groups 2 and 4 there was a significant increase in postoperative cortisol levels compared to initial values (p: 0.003, 0.008 respectively). Postoperative cortisol values of control groups (groups 2 and 4) had significantly higher cortisol levels compared to groups 1 and 3 (p: 0.034).

Stress response to surgical interventions is characterized by increased plasma levels of catecholamines, cortisol, prolactin, ADH, GH, glucose, lactate, pyruvate and some other hormones and their metabolites. Increased levels of these hormones and other related molecules are related with the severity of surgical intervention.

Intraabdominal surgeries usually cause more severe stress responses compared to superficial surgeries.
Intravenous or inhalation anesthetics might also increase plasma levels of these stress hormones. This increase is an undesired side effect as this situation might cause not only hemodynamic instability but also intraoperative and postoperative catabolism.

Some modifications in anesthesia protocols are being researched by clinicians to decrease incidence of these complications. In this study we examined a group of laparoscopic cholecystectomy patients for effects of adding esmolol in anesthesia protocol on serum prolactin and cortisol levels. We observed that in patients who received esmolol, serum cortisol levels significantly decreased postoperatively possibly indicating a decreased sympathetic activity. However there was a significant increase postoperative prolactin levels without any statistical difference between study groups.

When we compared study groups in means of hemodynamic parameters we also observed that intraoperative heart rates were significantly lower in esmolol groups (group 1 and 3) compared to their controls. Comparison of esmolol groups with controls in means of anesthetic - analgesic requirements revealed that there is a significant decrease in desflurane, propofol and remifentanil requirements.

Effects of β blockers in angina pectoris, hypertension and arhythmia are very well known. Using propranolol to decrease intraoperative myocardial ischemia in high risk patients is a common practice for anesthesiologists. However long half life of propranolol limits its usage. Esmolol is an ideal β blocker that has shorter half life and higher cardioselectivity. Its effect start fast and also gets eliminated in a short time with a half life of 9.2 ± 2 minutes. It shows its maximal effect on heart rate and blood pressure in 1-2 minutes after intravenous injection. Esmolol could be used by intravenous infusion or boluses due to its pharmacodynamic and pharmacokinetic properties.

Esmolol suppresses adrenergic response against laryngoscopy, tracheal intubation-exubation and peritoneal irritation due to CO₂ insufflation during laparoscopy. Using esmolol infusion intraoperatively gives opportunity to control sympathetic system response and there by decrease myocardial O₂ consumption. Depending on our findings we think that by close hemodynamic follow-up and titrating esmolol doses, anesthesiologist could avoid unwanted side effects of esmolol like hypotension, and also could use this dose titration advantage and decreased intraoperative heart rates to decrease myocardial O₂ requirements. Supporting our findings Smith and colleagues compared esmolol and alfentanil in means of hemodynamic stability in a group of arthroscopic surgery patients and reported that esmolol is a good alternative with less side effects.

We observed that addition of esmolol decreases remifentanil requirements significantly. In some studies remifentanil was reported to cause hypotension. Hogue and colleagues reported that 20% of patients who received remifentanil developed hypotension. Schuttler and colleagues and McAtamney and colleagues also reported similar results in two different studies. Depending on these findings we believe that adding esmolol in anesthesia protocols with remifentanil will significantly decrease hemodynamic complications and hypotension. According to our findings addition of esmolol also decreases requirements for propofol and desflurane. It could easily be foreseen that decreased anesthetic requirements will cause less side effects and also a decrease in economical cost. Supporting our findings Johansen and colleagues reported similar results. They compared effect of esmolol addition on propofol and 60% N₂O requirements and observed that esmolol significantly decreases requirements for both agents.

Main purpose of our study was to compare pre and postoperative levels of cortisol and prolactin in a group of patients who received or did not receive esmolol as a part of anesthesia protocol. We observed that prolactin levels significantly increased postoperatively in all groups compared to preoperative levels. We also observed a significant decrease in cortisol levels postoperatively in group 1 compared to preoperative levels. In groups 2 and 4 there was a significant increase in postoperative cortisol levels compared to initial values (Table 1). Effects of opioid agents on stress hormone response differs. Underlying mechanism of inhibition of stress response by high dose opioids is still not clear. Exogenous narcotic analgesics play regulatory roles in synthesis of many hypothalamic hormones. Fentanyl and new generation opioids
decrease stress response more efficiently compared to morphine. Fentanyl decreases hyperglycemic reaction and also decreases cortisol and growth hormone levels. Fentanyl has a similar effect with morphine in means of increasing plasma catecholamine levels but contradictorily decreases plasma anti diuretic hormone and renin. New generation opioids like sufentanil, alfentanil and remifentanil were reported to be more efficient in means of these findings.

However in our study we observed an increase in cortisol levels in groups 2 and 4 who received higher doses of remifentanil compared to esmolol receiving patients. On the other hand in those patients who received esmolol we observed a significant postoperative decrease in cortisol levels. Depending on these findings we believe that esmolol is not only more efficient in means of decreasing stress response but also might decrease anesthesia cost by decreasing anesthetic requirements.

Since 1950’s both ACTH and prolactin have been known to be secreted from hypophyseal gland as a stress response. Opioid receptors are thought to play role in secretion of prolactin. Endogenous opioids like morphine, Met-enkephalin and β endophine all cause an increase in prolactin secretion, on the other hand naloxone was reported to decrease secretion.

Nearly all studies in this subject was about evaluation of hormonal stress response but a few of them evaluated both hormonal response and hemodynamic parameters. Evaluation of adrenalin and noradrenalin levels after sympathetic induction by laryngeal intubation is also the most commonly used method in these studies. Previous studies reported that high or even medium doses of opioid analgesics like fentanyl are highly efficient in suppressing catecholamine discharge and decreased adrenalin and noradrenalin levels after sympathetic induction. Sahin and colleagues who evaluated hemodynamic responses against fentanyl and remifentanil reported a significant increase in prolactin levels of patients who received fentanyl. Song et al also compared fentanyl and remifentanil and reported that remifentanil was more efficient in suppressing endocrine stress response compared to fentanyl. Despite of these findings remifentanil was also reported in several other studies to increase stress hormone levels in similar way to endogenous opioids like morphine. In our study despite of lower doses of remifentanil in groups 1 and 3 we observed a similar increase in postoperative prolactin levels in all study groups. Depending on these findings we think that decreasing remifentanil dose by co administration of esmolol does not have a significant effect on decreasing postoperative prolactin response.

As a conclusion we observed that using adjuvant esmolol during anesthetic maintenance of laparoscopic cholecystectomy patients decreases anesthetic – analgesic requirements without causing any hemodynamic instability, and suppresses postoperative cortisol response but does not have any significant effect on postoperative prolactin response.

Preliminary data for this study were presented as a poster presentation at 48th Annual meeting of Turkish Society of Anesthesiology and Reanimation, 25-29 October 2014, Ankara, Turkey

REFERENCES


