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SCIENTIFIC ARTICLE

# Effect of intraoperative esmolol infusion on anesthetic, analgesic requirements and postoperative nausea-vomitting in a group of laparoscopic cholecystectomy patients

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**KEYWORDS**
Esmolol;
Postoperative pain;
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**Abstract**
*Purpose:* Postoperative pain and nausea/vomitting (PNV) are common in laparoscopic cholecystectomy patients. Sympatholytic agents might decrease requirements for intravenous or inhalation anesthetics and opioids. In this study we aimed to analyze effects of esmolol on intraoperative anesthetic-postoperative analgesic requirements, postoperative pain and PNV.
*Methods:* Sixty patients have been included. Propofol, remifentanil and vecuronium were used for induction. Study groups were as follows; I – Esmolol infusion was added to maintenance anesthetics (propofol and remifentanil), II – Only propofol and remifentanil was used during maintenance, III – Esmolol infusion was added to maintenance anesthetics (desflurane and remifentanil), IV – Only desflurane and remifentanil was used during maintenance. They have been followed up for 24 h for PNV and analgesic requirements. Visual analog scale (VAS) scores for pain was also been evaluated.
*Results:* VAS scores were significantly lowest in group I ($p = 0.001–0.028$). PNV incidence was significantly lowest in group I ($p = 0.026$). PNV incidence was also lower in group III compared to group IV ($p = 0.032$). Analgesic requirements were significantly lower in group I and was lower in group III compared to group IV ($p = 0.005$). Heart rates were significantly lower in esmolol groups (group I and III) compared to their controls ($p = 0.001$) however blood pressures were similar in all groups ($p = 0.594$). Comparison of esmolol groups with controls revealed that there is a significant decrease in anesthetic and opioid requirements ($p = 0.024–0.03$).
*Conclusion:* Using esmolol during anesthetic maintenance significantly decreases anesthetic-analgesic requirements, postoperative pain and PNV.


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**PALAVRAS-CHAVE**
Esmolol;
Dor no pós-operatório;
Vômito no pós-operatório

**Efeito da infusão de esmolol sobre a necessidade de anestesia no intraoperatório e analgesia, náusea e vômito no pós-operatório em um grupo de pacientes submetidos à colecistectomia laparoscópica**

**Resumo**
*Objetivo:* A dor e a incidência de náusea e vômito no período pós-operatório (NVP) são comuns em pacientes submetidos à colecistectomia laparoscópica. Os agentes simpatolíticos podem diminuir a necessidade de opiáceos ou anestésicos inalatórios ou intravenosos. Neste estudo, nosso objetivo foi analisar os efeitos de esmolol sobre a necessidade de anestésico no período intraoperatório e de analgésico no pós-operatório e a incidência de dor e NVP.
*Métodos:* Sessenta pacientes foram incluídos. Propofol, remifentanil e vecurônio foram usados para a indução. Os grupos de estudo foram os seguintes: grupo I, a infusão de esmolol foi adicionada aos anestésicos (propofol e remifentanil) para manutenção; grupo II, apenas propofol e remifentanil foram usados durante a manutenção; grupo III, a infusão de esmolol foi adicionada aos anestésicos (desflurano e remifentanil) para manutenção; grupo IV, apenas desflurano e remifentanil foram usados durante a manutenção. O período de acompanhamento foi de 24 horas para avaliar a incidência de NVP e a necessidade de analgésicos. Os escores de dor também foram avaliados por meio da Escala Visual Analógica (EVA).
*Resultados:* Os escores EVA foram significativamente menores no grupo I ($p = 0{,}001-0{,}028$). A Incidência de NVP foi significativamente menor no grupo I ($p = 0{,}026$). NVP também foi menor no grupo III em relação ao grupo IV ($p = 0{,}032$). A necessidade de analgésicos foi significativamente menor no grupo I e menor no grupo III em relação ao grupo IV ($p = 0{,}005$). A frequência cardíaca foi significativamente menor nos grupos esmolol (grupos I e III) comparados aos controles ($p = 0{,}001$), mas a pressão arterial foi semelhante em todos os grupos ($p = 0{,}594$). A comparação entre os grupos esmolol e controles revelou que houve uma diminuição.
*Conclusão:* O uso de esmolol durante a manutenção da anestesia reduz significativamente a necessidade de anestésico-analgésico, dor e incidência de NVP.


## Introduction

Laparoscopic cholecystectomy became a daily routine procedure with low cost and high patient satisfaction by developments in surgical and anesthetic techniques. Despite of high success rates in postoperative pain and nausea-vomitting (PNV) are still important problems that delay patient discharge. Intra and postoperative hemodynamic stability and efficient analgesia might prevent these complications. In these patients hemodynamic stress responses like hypertension and tachycardia might develop as a reflex to endotracheal intubation or surgical intervention itself. Insufflation of carbondioxide into peritoneal cavity might also trigger this response. Plasma concentrations of stress hormones might also increase secondary to side effects of some anesthetic agents. Hemodynamic instability is an important triggering factor for PNV.[1] Different techniques or anesthetic agents could be used to decrease hemodynamic response and related postoperative complications.[2–4] Increasing volatile anesthetic concentrations and/or opioid usage are some methods that could be preferred.[2] However intraoperative opioids might also delay postoperative recovery and increase PNV rates. 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.[2–8] In this study we aimed to analyze effects of esmolol, a cardioselective beta-1 ($\beta_1$) adrenergic receptor antagonist, on intraoperative anesthetic–postoperative analgesic requirements, postoperative pain and PNV.

## Methodology

Study was designed as a prospective study after approval from local ethical committee (KA174-09012013). 60 patients aged between 18 and 60 years who underwent laparoscopic cholecystectomy have been included. Exclusion criterias 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 $\beta$ blockers or calcium channel blockers. No premedications were used before operation. Electrocardiographic (ECG), invasive intraarterial blood pressures, MBP, peripheral oxygen saturations ($SpO_2$) vs. bispectral index (BIS) monitorizations were done and recorded as study data. Propofol 2.5 mg/kg, remifentanil 1 $\mu$g/kg and vecuronium 0.1 mg/kg were used for induction in all patients. 50% $O_2$ and fresh air mixture was used during mechanical ventilation. End-tidal $CO_2$ ($ETCO_2$)

levels were aimed to be between 35 and 45 mmHg and fresh gas flow rate was 3 L/min in all patients.

Study groups were as follows:

**Group I**: After induction, 5 min 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 II**: Maintenance anesthetics were 75–85 μg/kg/min propofol and 0.2 μg/kg/min remifentanil. No esmolol infusion was used.

**Group III**: After induction, 5 min 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 μ/kg/min remifentanil.

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

Group II was designed as control for group I and group IV was designed as control for group III. 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 min after surgery. Postoperative ECG, MBP, heart rates, peripheral $SpO_2$ monitorizations were done and recorded as study data. 0.5 mg/kg tramadol was given to patients with >3 points in visual analog scale (VAS) evaluations. 10 mg metoclopramide IV was applied to al 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 h for PNV and analgesic requirements. VAS was also been reevaluated at 12th and 24th hours and scores were recorded as study data.

## Statistical methodology

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. 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

60 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) chatracteristics (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 I and group II compered to groups III and IV (Table 1). These durations were similar when esmolol groups were compared with only their controls (group I vs. II and group III vs. IV). Mean BIS values were similar between groups and were between 40 and 60 ($p = 0.270$). VAS score measured in PACU, 12th and 24th postoperative hours were significantly lowest in group I ($p = 0.001$, 0.003, 0.028 respectively). PNV incidence in postoperative 24 h was significantly lowest in group I compared to all other groups ($p = 0.026$). However PNV incidence was also lower in group III compared to its' control, group IV ($p = 0.032$). Similarly analgesic requirements in postoperative 24 h were significantly lower in group I compared to all other groups and was lower in group III compared to its' control, group IV ($p = 0.005$). When compared in means of hemodynamical parameters heart rates were significantly lower in esmolol groups (group I and III) 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 desfluran, propofol and remilfentanil requirements ($p = 0.024$, 0.03, 0.026 respectively).

## Discussion

Despite of high success rates in laparoscopic cholecystectomy procedures, postoperative pain and PNV are still common problems. Efficient postoperative analgesia and intraoperative hemodynamic stability are very important factors that affect complication rates in these patients.[9] PNV has an incidence 40–75% and usually delays patient discharge.[9,10] Female gender, smoking, previous PNV history, carsickness history, postoperative opioid usage, intraoperative hypotension and orthostotic hypotension are major risk factors for PNV.[11–13]

Some modifications in anesthesia protocols are being researched by clinicians to decrease incidence of these complications. In this study we observed that decreasing opioid and anesthetic doses and addition of esmolol into anesthesia protocol decreases PNV rates and postoperative pain comlication rates without causing any significant hemodynamic complication. Using high opioid doses in daily laparascopic procedures might cause a delay in recovery duration, increased PNV and urinary retention rates. Beta blockers could be used effectively as alternative agents to decrease opioid requirements. Possible positive effects of beta blockers are hemodynamic stability, decreased anesthetic and analgesic requirements, decreased PNV rates and decreased intubation stress.

Effects of beta blockers in angina pectoris, hypertension and arrythmia are very well known.[14,15] Using propranolol

**Table 1** Comparison of study groups.

| | Group I ($n=12$) | Goup II ($n=15$) | Group III ($n=21$) | Group IV ($n=12$) | $p$-Value |
|---|---|---|---|---|---|
| Gender (F/M) | 9/3 | 12/3 | 15/6 | 8/4 | 0.724 |
| Gender (years) | 44.3 ± 13.2 | 45.3 ± 14.2 | 51.7 ± 9.3 | 48.8 ± 11.9 | 0.318 |
| Surgery duration (min) | 79.1 ± 23.9 | 82.6 ± 31.3 | 62.2 ± 24.1 | 55.5 ± 23.5 | 0.054 |
| Anesthesia duration (min) | 92.1 ± 25.6 | 91.1 ± 35.7 | 77.7 ± 22.9 | 68.1 ± 24.8 | 0.097 |
| Postoperative VAS (in PACU) | 0.5 (1) | 3 (2) | 2 (1) | 3 (2) | 0.001 |
| Postoperative VAS (12th hours) | 0.5 (1) | 2 (2) | 2 (1.5) | 2.5 (2) | 0.003 |
| Postoperative VAS (24th hours) | 0 (0) | 1 (2) | 1 (2) | 0.5 (2.75) | 0.028 |
| Analgesia requirement in postoperative 24 h | 2/12 (16.7%) | 10/15 (66.7%) | 5/21 (23.8%) | 8/12 (66.7%) | 0.005 |
| PNV in postoperative 24 h | 1/12 (8.3%) | 6/15 (40%) | 7/21 (33.3%) | 8/12 (66.7%) | 0.03 |
| Intraoperative heart rate (pulse/min) | 66.4 ± 9.1 | 77.4 ± 7.5 | 69.3 ± 6.4 | 72.8 ± 6.1 | 0.001 |
| Intraoperative mean blood pressure (mmHg) | 91 ± 15.7 | 92.1 ± 11.7 | 91.6 ± 8.3 | 86.6 ± 10.8 | 0.594 |
| Heart rate in PACU (pulse/min) | 63.6 ± 11.9 | 72.9 ± 12.4 | 67.4 ± 12.1 | 65.7 ± 15.6 | 0.327 |
| Mean blood pressure in PACU (mmHg) | 79.7 ± 15.1 | 89.1 ± 16.3 | 80.9 ± 13 | 76.8 ± 9.5 | 0.094 |
| Mean BIS value | 51.9 ± 20.2 | 51.7 ± 12.6 | 46.7 ± 9.4 | 43.4 ± 8.5 | 0.270 |
| Propofol requirements (mL) | 328.4 ± 173.8 | 530.1 ± 244.1 | – | – | 0.024[a] |
| Desflurane requirements (mL) | – | – | 31.2 ± 12.3 | 43.6 ± 18.9 | 0.03[b] |
| Remilfentanil requirements (mL) | 174.6 ± 100.8 | 269.2 ± 105.2 | 132.9 ± 146.0 | 562.4 ± 152.4 | 0.026[a] 0.0001[b] |

[a] $p$-Value between group 1 and 2.
[b] $p$-Value between group 3 and 4.

to decrease intraoperative myocardial ischemia in high risk patients is a common practice for anesthesiologists. However long half life of propranalol limits its' usage. Esmolol is an ideal beta blocker that has shorter half life and cardioselectivity. Its' effect start fast and also gets eliminated in a short time with a half life of 9.2 ± 2 min.[16] It shows its' maximal effect on heart rate and blood pressure in 1–2 min after intravenous injection.[17] Esmolol could be used by intravenous infusion or boluses due to its' pharmacodynamic and pharmacokinetic properties. Esmolol supresses adrenergic response against laryngoscopy, tracheal intubation–extubation and peritoneal irritation due to $CO_2$ insufflation during laparoscopy. Using esmolol infusion intraoperatively gives opportunity to control sympathetic system response and there by decrease myocardial $O_2$ consumption.[18–21] It was also reported to decrease perioperative nausea response.[22]

In patients who received esmolol with standart anesthesia protocol (groups I and III) we observed that intraoperative heart rates were significantly lower, however there was no significant difference in intraoperative MBP compared to control groups. We also observed that there was no significant difference between study groups and controls in means of heart rates and blood pressure during recovery phase in PACU. Depending on these 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 $O_2$ requirements. Supporting our findings Smith and colleques compared esmolol and alfentanil in means of hemodynamic stability in a group of arthroscopic surgery patients and reported that esmolol as a good alternative with less side effects.[1] Coloma and colleques also compared esmolol with remilfentanil in means of hemodynamic stability in a group of laparascopic gynecological surgery patients and reported it provides a beter hemodynamic stability.[5]

Remifentanil is a synthetic opioid agonist. Its' effects reaches maximal levels in a relatively short period of time. It is eliminated by tissue and blood esterases and has a very short half life.[23] Because of these properties remifentanil is a good alternative for fentanyl.[24] However, in some studies remifentanil was reported to cause hypotension. Hogue and colleques reported that 20% of patients who received remifentanil developed hypotension.[25] Schuttler and colleques and McAtamney and colleques also reported similar results in two different studies.[26,27] In our study we observed that addition of esmolol decreases remifentanil requirements significantly. 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 colleques reported similar results. They compared effect of esmolol addition on propofol and 60% $N_2O$ requirements and observed that esmolol significantly decreases requirements for both agents.[7] In two different studies Topçu et al.[28] and Wilson et al.[29] reported esmolol decreased both propofol and remifentanil requirements. Chia and colleques reported that addition of esmolol decreases anesthetic requirements

and also postoperative analgesia and morphine usage.[30] Moon and colleques reported that using esmolol might decrease PACU recovery duration in gynecological surgery patients.[6]

In this study we observed that besides lowering anesthetic requirements adjuvant esmolol also decreases analgesic requirements and VAS scores in postoperative 24 h. Some previous studies also supported our findings. Bhawna and colleques reported that in lower abdominal surgery patients addition of esmolol to isoflurane might decrease both anestetic and postoperative analgesic requirements.[31] Öztürk and colleques reported that both PNV incidence and analgesic requirements decrease in laparoscopic cholecystectomy patients by adjuvant esmolol. Two similar studies also reported a decrease in postoperative pain and analgesic requirements.[8] Previous studies demonstrated emotional stress, fear and anxiety triggers hippocampal activation in magnetic resonance imaging. These changes were hought to be secondary to a neuroactive substance like norepinephrine. Hippocampal N-methyl-D-aspartate (NMDA) and adrenergic receptors are thought to play role in perception. Blockage of these receptors may decrease activation of adrenergic activity and so pain.[32] Beta blockers might also decrease hepatic blood flow and metabolism of both their and other drugs and as a result might decrease postoperative analgesic requirements.[33,34]

Another finding we observed in our study was decreased PNV and antiemetic requirements in patients who received esmolol. Hypertensive patients or the ones who develop postoperative hypotension were reported to have increased PNV incidence compared to other populations.[35] For this purpose hemodynamic stability during and just after surgery is important to prevent PNV.[36] From this perspective we found that patients who received esmolol did not have any blood pressure abnormality (hypo or hypertension) and also required lower doses of opioid agents, which are well known nausea and vomitting triggering agents. We think that these might be the cause of decreased PNV rates in these patients. However there is conflicting findings in literature that evaluated the relationship between esmolol and PNV. Öztürk and colleques and Coloma and colleques reported similar findings with our study.[5,8] On the other hand Smith and colleques did not observe any superiority of esmolol in means of PNV.[1]

Main purpose of this study was observing and comparing effects of adding esmolol to standart anesthetic protocols. On the other hand we also had opportunity to compare propofol-remifentanil based and desflurane-remifentanil based anesthesia protocols. According to our findings VAS score measured in PACU, 12th and 24th postoperative hours were significantly lowest in group I (propofol-remifentanil after esmolol). PNV incidence in postoperative 24 h was also significantly lowest in group I compared to all other groups. Similarly analgesic requirements in postoperative 24 h were significantly lower in these patients compared to all other groups. Depending on these findings we think that propofol based anesthesia protocols might be advantageous compared to desflurane based protocols. Supporting our findings Song et al. reported that propofol was significantly more effective compared to desflurane in means of preventing PNV.[37] However in means of pain prevention there are some data in literature that contradicts our findings. Hepağuşlar et al., Fassoulaki et al., Ortiz et al. reported that there is no significant difference between propofol and sevoflurane or desflurane based anesthetic protocols in means of post operative pain prevention in 3 different studies.[38–40] This field needs more studies for clarification.

As a conclusion we observed that using adjuvant esmolol during anesthetic maintenance of laparoscopic cholecystectomy patients decreases anesthetic–analgesic requirements, postoperative pain and PNV without causing any hemodynamic instability. We also observed that propofol-remifentanil based anesthesia protocols might be advantageous in means of PNV and pain prevention compared to desflurane-remifentanil based protocols.

## Conflicts of interest

The authors declare no conflicts of interest.

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