Original Article

The effect of esmolol compared to opioids on postoperative nausea and vomiting, postanesthesia care unit discharge time, and analgesia in noncardiac surgery: A meta-analysis

Venkatesan Thiruvenkatarajan, Richard Watts, Marni Calvert[1], Graeme Newcombe, Roelof Markus Van Wijk

Department of Anaesthesia, The Queen Elizabeth Hospital, Woodville South 5011, [1]Department of Anaesthesia, The Royal Adelaide Hospital, North Terrace, The Discipline of Acute Care Medicine, The University of Adelaide, Adelaide, South Australia

Abstract

Background and Aims: Perioperative esmolol as an opioid alternative has been shown to reduce postoperative nausea vomiting using opioid sparing. The aim of this meta-analysis was to compare esmolol and opioids on postoperative nausea and vomiting (PONV), time spent in recovery, and analgesia in noncardiac surgeries.

Material and Methods: OVID Medline (1980–February 2014), OVID EMBASE, EBSCO, CINAHL, and the Cochrane Register of Controlled Trials were searched for randomized controlled trials (RCTs) comparing esmolol and opioids on early postoperative recovery and pain intensity during general anesthesia in noncardiac surgeries. The primary outcomes were related to PONV and postanesthesia care unit (PACU) discharge time, whereas secondary outcomes were related to early postoperative pain.

Results: Eight trials were identified involving 439 patients, 228 of whom received esmolol while 211 received opioids. A random-effects meta-analysis showed that in comparison with opioids, esmolol led to a 69% reduction in the incidence of PONV (odds ratio 0.31, 95% confidence interval [CI] 0.13–0.74, $P = 0.008$, $I^2 = 44.1\%$). An increase in the volatile anesthetic requirement was evident in the esmolol group compared with opioid (MD + 0.67% desflurane equivalent, 95% CI 0.27–1.08, $P = 0.001$, $I^2 = 23.5\%$). There was no statistically significant difference between the esmolol and opioid groups in relation to PACU discharge time, early postoperative pain scores, opioid requirement, and cumulative opioid consumption. Significant heterogeneity was noted between studies. No significant adverse effects were noted.

Conclusion: Compared with opioids, perioperative esmolol may reduce the incidence of postoperative nausea vomiting and increase the volatile anesthetic requirement. Esmolol administration may not improve the early postoperaive pain intensity. Nonetheless, these findings are limited by the absence of high-quality RCTs and the heterogeneity among studies. Further, large-scale studies are needed to explore these results.

Keywords: Analgesia, esmolol, opioids, recovery

Introduction

Postoperative nausea and vomiting (PONV) and inadequate analgesia are some of the known impedances of early recovery from general anesthesia. A multimodal approach using a diverse group of medications is likely to improve postoperative analgesia, spare opioids, and enable smooth recovery.[1,2] There is greater emphasis to employ nonopioid intraoperative adjuncts in fast-track and ambulatory surgery.[1] Esmolol, a cardioselective ultrashort-acting β-blocker has been shown to be an effective alternative to the use of intraoperative opioids, thereby reducing the opioid-related side effects and assisting early postoperative recovery.[2,3]

Address for correspondence: Dr. Richard Watts, Department of Anaesthesia, The Queen Elizabeth Hospital, 28 Woodville Road, Woodville South 5011, Adelaide, South Australia. E-mail: Richard.Watts@health.sa.gov.au

Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/0970-9185.209747

How to cite this article: Thiruvenkatarajan V, Watts R, Calvert M, Newcombe G, Van Wijk RM. The effect of esmolol compared to opioids on postoperative nausea and vomiting, postanesthesia care unit discharge time, and analgesia in noncardiac surgery: A meta-analysis. J Anaesthesiol Clin Pharmacol 2017;33:172-80.

Various experimental and clinical data on animals as well as humans have shown that β-blockers including esmolol have anesthetic- and analgesic-sparing effects.[2-14] A few studies have directly compared esmolol against other intraoperative opioids producing results in favor of esmolol relating to opioid sparing and early recovery.[2,3] A previous limited meta-analysis has shown that esmolol reduces the incidence of PONV, reduces the time spent in the postanesthesia care unit (PACU), and increases the postoperative opioid requirement.[15]

This meta-analysis was designed to assess the efficacy of esmolol versus opioids on PONV and analgesia in noncardiac surgeries. Our primary aim was to analyze the effects on smooth outcome from general anesthesia such as PONV and time spent in the PACU. Our secondary aim was to analyze its impact on early postoperative pain intensity, opioid sparing, and intraoperative anesthetic requirements.

Material and Methods

Literature search

The review was conducted as per the recommendations of the PRISMA statement (www.prisma-statement.org). The electronic databases, OVID Medline (1980–February 2014), OVID EMBASE, EBSCO, CINAHL, and the Cochrane Register of Controlled Trials for randomized controlled trials (RCTs) were searched for trails that compared esmolol with opioids in adults undergoing general anesthesia. Databases were searched using the Medical Subject Headings term "esmolol" used in conjunction with "pain scores;" "analgesia requirement;" "postoperative nausea and vomiting" (PONV); and postanesthesia recovery unit ("PACU") "discharge time." The search further included a set of items using the esmolol set in conjunction with opioid drugs, including "morphine," "fentanyl," "remifentanil," "oxycodone," "alfentanil," "pethidine" and "sufentanil," and a further set using the terms "propofol," "isoflurane," "desflurane," "halothane," and "sevoflurane." No language restriction was applied. Additional articles were identified through the bibliographies of relevant studies. The manufacturers of esmolol were contacted for unpublished studies but reported none.

Study eligibility and validity scoring

Only RCTs on esmolol versus intraoperative opioids for noncardiac surgeries where at least one outcome variables such as PONV, PACU discharge times, pain scores, postoperative opioid consumption, and intraoperative anesthetic requirement were reported were included in the meta-analysis. Studies that compared esmolol as an adjunct were excluded. Trials investigating the effect of esmolol on intraoperative arrhythmias, attenuation of hemodynamic responses to laryngoscopy or surgery, intracranial pressure, electroconvulsive therapy, bispectral index (BIS) attenuation, and cardiovascular morbidity and mortality were excluded from the study unless one of the outcome variables of interest was also reported.

Three review authors (Richard Watts, Venkatesan Thiruvenkatarajan, and Marni Calvert) assessed the methodological quality of the included studies using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. The risk of bias was assessed under the following domains: random sequence generation, allocation concealment, blinding of participants, personnel and outcome measures, incomplete outcome data, selective reporting, and other biases.

Data abstraction and defining outcome parameters

A standardized data extraction form was designed, and the data were extracted by three review authors (Richard Watts, Marni Calvert and Venkatesan Thiruvenkatarajan). For every included study, the following demographic characteristics were collected: mean age, mean weight, American Society of Anesthesiologists (ASA) status, type of surgery, and the total number of patients involved. The intraoperative study data extracted were esmolol loading dose, infusion rate and total dose, use of BIS, use of nitrous oxide, and antiemetic prophylaxis. Postoperative nausea vomiting, PACU discharge time, postoperative pain scores, opioid usage, requirement for rescue opioid and anesthetic requirement, and the use of adjuvant analgesic agents were also recorded. Each of the included studies was analyzed for esmolol-related adverse effects, including hypotension and bradycardia as reported requiring intervention. Data were originally extracted from text or tables of the articles. If the data were missing, the authors were contacted. If they did not respond, the data were extrapolated from graphs. Differences were resolved by agreement within the group.

The primary outcomes were PONV in PACU and PACU discharge time. Secondary outcomes were pain scores at rest in PACU, cumulative opioid consumption, rescue analgesic administration, intraoperative anesthetic requirement, and adverse events such as bradycardia and hypotension. Studies addressing one or more of these outcomes were included in the analysis.

Definition of PONV and PACU discharge time were extracted as reported in the original studies. PACU discharge time was recorded in minutes as the time spent in PACU. For pain intensity, visual analog score (VAS) or numeric rating scale (NRS) of pain at rest were converted to a

0–10 NRS. The first reported pain scores within 4 h after surgery were extracted. When it was unclear as to whether the pain scores were assessed at rest or movement, we assumed that the scores were evaluated at rest. Postoperative cumulative opioid consumption as described by studies was converted to equianalgesic dose of intravenous morphine [Appendix 1]. Postoperative opioid rescue requirement was expressed as the number of subjects requiring rescue analgesics in the PACU. Volatile anesthetic usage was defined as the minimal alveolar concentration (MAC %) required for anesthetic maintenance and converted to desflurane equivalence using an MAC equivalent conversion chart [Appendix 1].

The loading dose of esmolol was documented as actual (reported) or calculated to mean body weight, whereas the infusion rate was either the actual or the range used (μg/kg/min).

Statistical analysis

All analyses were done using the statistical package R (The R Foundation for Statistical Computing, c/o Institute for Statistics and Mathematics, Wirtschaftsuniversitaet Wien, Welthandelsplatz 1, 1020 Vienna, Austria) and Metafor (Meta-Analysis Package for R). A meta-analysis was done when the outcome variables were reported by two or more trials.

Means, standard deviations (SDs), and sample sizes were extracted for each of the randomized groups for continuous outcomes. When medians and ranges were reported, the mean was assumed to be equal to the median and the SD equal to the range divided by four. Weighted means and pooled SDs were calculated while combining results across separate groups within a study. In the case of binary outcomes, numerators and denominators were extracted for each of the randomized groups. The differences between randomized groups in continuous and binary outcomes were pooled across studies using random-effects meta-analysis models. The differences in means between groups were chosen as the effect measure of interest for continuous outcomes while for binary outcomes the odds ratio (OR) was used. Heterogeneity in mean differences and OR were assessed using the I^2-test and Chi-square test goodness of fit tests.

Results

Included studies

From the 338 studies identified, eight RCTs comparing esmolol versus opioids were included in this meta-analysis with a total of 439 participants, 228 receiving esmolol, and 211 opioids [Figure 1]. The range of trial sample sizes was 28–97 participants [Table 1]. One trial was accessible in Korean,[16] and one study was analyzed from an abstract data.[17]

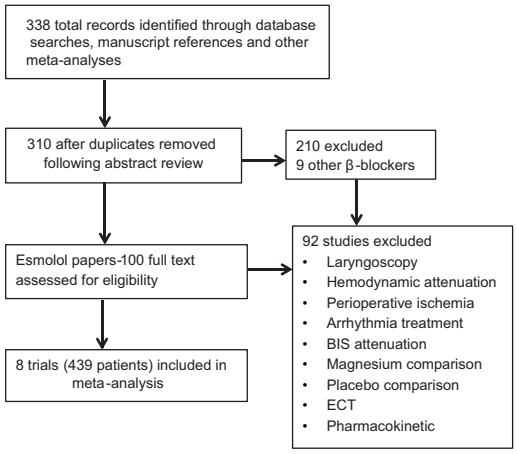

Figure 1: PRISMA flow chart describing retrieved, excepted, assessed, and included trials

All trials enrolled ASA Grade I–II patients except for one where ASA III patients were included in the study.[17] There were six laparoscopic procedures of which three were ambulatory,[2,3,18] one each of general surgery,[19] and arthroscopic procedures.[20]

A loading dose of esmolol followed by an infusion was employed in all studies except one where a loading dose was followed by rescue bolus doses.[17] The most common loading dose were 0.5 or 1 mg/kg, given just before induction while infusion rates varied between 5 and 300 μg/kg/min. Esmolol administration was targeted to predetermined hemodynamic endpoints in all, but one trial that evaluated the effects of esmolol on emergence phenomenon.[19] The total esmolol dose ranged between 23 and 1623 mg. Nitrous oxide use was reported in four studies, and similarly, prophylactic antiemetics were administered in four trials [Table 1]. Remifentanil was the intraoperative opioid that was compared against esmolol in four studies, alfentanil, and fentanyl in two studies each [Table 1].

Risk of bias assessment

A low risk of bias according to the Cochrane risk of bias assessment tool was noted in only one trial (12%) [Table 2]. Random sequence generation was described in four trials; allocation concealment was properly described in one study. Participants and personnel were unblinded in six studies; outcome assessment was unblinded in four trials. Incomplete outcome data were not adequately addressed in five studies, and selective outcome reporting was not properly addressed in three studies [Table 2].

Primary outcomes

Postoperative nausea and vomiting

Data on the incidence of PONV could be assessed from six studies.[2,3,16-19] A 69% of reduction in the

Table 1: Study characteristics

Studies	Total patients (*n*)	Treatment groups	Mean age (years)	Mean weight (kg)	Surgery	Loading dose (mg/kg)	Infusion rate (μ/kg/min)	Total dose (mg)	Multimodal analgesia	BIS	Nitrous oxide	Anti-emetic prophylaxis	Comments
Lazo *et al.*[17] (abstract)	43	Esmolol (*n*=20) Fentanyl (*n*=23)	49±11 48±13	-	Laparoscopic gastrointestinal	0.5	Rescue 10 mgbolus doses only	64.5±33 23.57±9	Yes	Yes	No	Yes	Rescue hydromorphone
López-Álvarez *et al.*[10]	60	Esmolol (*n*=30) Remifentanil+ketamine (*n*=30)	55±16 56±12	-	Laparoscopic cholecystectomy	0.5	5-15	-	Yes	Yes	No	Yes	Pain VAS at 2 h 70 kg weight assumed
Lee *et al.*[16]	80	Esmolol (*n*=20) Esmolol+nicardipine (*n*=20) Control (*n*=20) Remifentanil (*n*=20)	38±7 40±8 42±10 40±9	56±6 56±7 62±8 56±9	Laparoscopic gynecological	1.0	5 5	92.7±18.8 76.3±9.3	Yes	Yes	No	No	Korean text English tables esmolol groups combined Nicardipine only at intubation
Collard *et al.*[2]	85	Esmolol (*n*=30) Control (*n*=27) Remifentanil (*n*=28)	47±16 53±17 48±18	71±14 74±15 68±16	Laparoscopic cholecystectomy	1.0	5-15	93.4±28.7	Yes	Yes	No	Yes	No intra - operative supplemental Fentanyl for esmolol group - pain scores in PACU
Coloma *et al.*[3]	53	Esmolol (*n*=27) Remifentanil (*n*=26)	29±5 29±6	72±17 74±14	Laparoscopic gynecological	1.0	5-15	126±78	Yes	Yes	Yes	Yes	Hydrocodone and fentanyl rescue calculated pain scores in PACU
Bagshaw *et al.*[18]	40	Esmolol (*n*=20) Fentanyl (*n*=20)	31±2 34±2	65±3 66±4	Laparoscopic gynecological	2.0	300	1623±70.1	Yes	No	Yes	No	No intraoperative Fentanyl in control group
Fuhrman *et al.*[19]	28	Esmolol (*n*=14) Alfentanil (*n*=14)	33±11 31±7	81±7 71±15	General	0.5	300	-	-	-	Yes		Emergence data only
Smith *et al.*[20]	97	Esmolol (*n*=47) Alfentanil (*n*=50)	37±14 36±13	80±14 81±4	Arthroscopic	2.0	25-100	360±100	Yes	No	Yes	No	VAS, PONV at discharge from PACU

Data are mean±SD, range or number as appropriate. PACU = Postanesthetic care unit, VAS = Visual analog score (pain), PONV = Postoperative nausea and vomiting, TCI = Target controlled infusion, SD = Standard deviation, BIS = Bispectral index

incidence was noted in patients who received esmolol compared with those who received an opioid (OR 0.31, 95% confidence interval [CI] 0.13–0.74, $P = 0.008$, $I^2 = 44.1\%$) [Figure 2]. A single,[2] dual,[17] and three[3] intraoperative antiemetics were administered in three studies each. The remaining three studies did not report the use of prophylactic antiemetics.[16,18,19]

Postanesthesia care unit discharge time

PACU discharge time data were available in six studies.[2,3,16-18,20] Pooled analysis showed no significant difference between the esmolol and the opioid groups in relation to the time they spent in the PACU (MD - 16, 95% CI − 39–7.0, $P = 0.181$; $I^2 = 97.7\%$) [Figure 2].

Secondary outcomes

Early postoperative pain intensity

Three trials reported data on postoperative pain intensity in PACU at various time points up to 3 h, verbal numerical rating scale was reported in two,[10,17] and VAS was reported in one.[20] None of the included studies described clearly whether the pain intensity was reported at rest or with movement. There was no statistically significant difference between esmolol and opioids in reducing the early postoperative pain intensity (MD - 0.19, 95% CI − 1.05–0.67, $P = 0.661$; $I^2 = 87.8\%$) [Figure 3]. Two studies[10,17] reported concomitant intraoperative nonsteroidal anti-inflammatory agents use, and the heterogeneity was noted to be high [Figure 3].

Postoperatiove opioid consumption

Three studies[2,10,17] reported the cumulative consumption of a variety of opioids in the PACU and one trial until 24 h after surgery.[3] There was no statistically significant difference between esmolol and opioids in postoperative opioid consumption in morphine equivalents (MD - 4.6 mg, 95% CI − 9.9–0.8, $P = 0.095$; $I^2 = 98.7\%$) [Figure 3]. Intraoperative nonsteroidal anti-inflammatory agents use was described in all the studies, and the heterogeneity was noted to be high.

Postoperative rescue analgesic requirement

Four studies reported on the use of rescue analgesics in the PACU. Intravenous fentanyl[3] and morphine[10] administration were described in two different trials, and the type of rescue was not described in the remaining two.[16,20] No significant difference in the requirement of rescue was noted between the esmolol and opioid groups (OR 0.65, 95% CI 0.13–3.31, $P = 0.606$, $I^2 = 87.3\%$) [Figure 3].

Volatile anesthetic requirement

The volatile anesthetic requirement data were accessible in three studies. Two studies[2,3] provided data on desflurane usage

Table 2: Risk of bias assessment of included studies

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Summary
Bagshaw *et al.*[18]	Low	Unclear	High	Low	Low	Low	Low	Unclear
Collard *et al.*[2]	Low	Unclear	High	Low	Low	Low	Low	Unclear
Coloma *et al.*[3]	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Lazo *et al.*[17]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Fuhrman *et al.*[19]	High	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Lee *et al.*[16]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
López-Álvarez *et al.*[10]	Low	Low	Low	Low	Low	Low	Low	Low
Smith *et al.*[20]	Unclear	Unclear	Low	Low	Unclear	Low	Low	Unclear

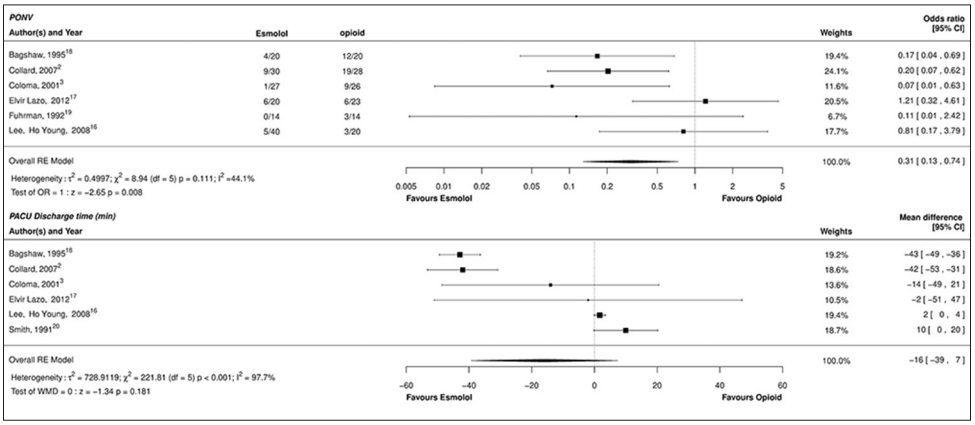

Figure 2: Forest plots for primary postoperative recovery outcomes: PONV = Postoperative nausea and vomiting; PACU = Post anesthesia care unit

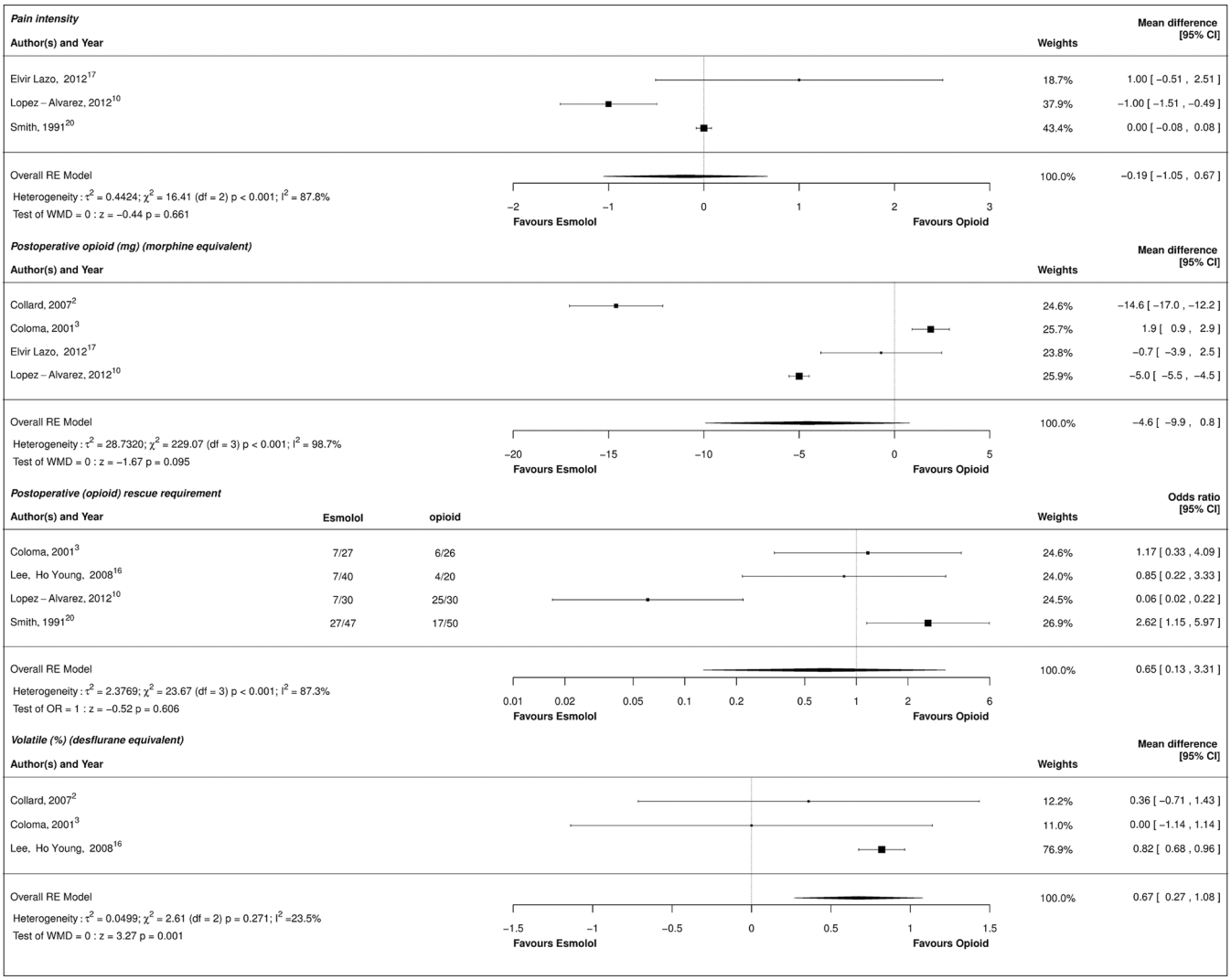

Figure 3: Forest plots for secondary postoperative pain outcomes: Pain intensity, cumulative opioid consumption, rescue analgesic, and volatile anesthetic requirement

as MAC-hour and the other study had described sevoflurane maintenance as volumes percent.[16] When esmolol was compared with opioid, volatile requirement was increased by MD + 0.67% desflurane equivalent (95% CI 0.27–1.08, $P = 0.001$, $I^2 = 23.5\%$) [Figure 3]. A low heterogeneity was noted.

Adverse events

No serious esmolol-related adverse events such as awareness, stroke, or severe hemodynamic instability were reported in the studies reviewed. Four studies reported nil occurrence of significant bradycardia and hypotension requiring intervention.[2,3,18,20] One study reported incidences of 6.6% and 10%, respectively of bradycardia and hypotension requiring interventions in the esmolol group.[10]

Discussion

This meta-analysis of eight underpowered, low-quality RCTs assessing the effects of intraoperative esmolol versus opioids shows that esmolol reduces the incidence of PONV despite increasing the volatile anesthetic requirement. No significant differences were found between esmolol and opioids regarding time spent in the PACU and early postoperative pain relief. Esmolol failed to improve the pain scores in recovery and had no impact on rescue analgesic requirement and cumulative opioid consumption.

The reporting of the incidence of PONV was quite consistent across the included studies with most of them defining it as a self-reported or assessed symptom before patients leaving the recovery room. The studies pooled for PONV analysis also included the trials that collectively showed that the volatile anesthetic use was increased when esmolol was substituted for an opioid.[2,3,16] Although it is well recognized that increased volatile use is a major risk factor for early PONV,[21] a paradoxical effect was noted in our analysis. The overall intraoperative avoidance of opioids is a plausible explanation for the PONV effect.

A limited systematic review on the safety of esmolol had shown a reduced incidence of PONV in esmolol-treated patients while comparing with opioids in attenuating the hemodynamic response to intubation and extubation.[15] Nevertheless, patients who received esmolol needed more opioids in the recovery room. A similar effect was not observed from our analysis. In contrast to our meta-analysis that failed to show an opioid sparing effect, a few studies have shown a positive effect when esmolol was used as an adjuvant during an opioid-based anesthesia.[4,5,7,9,11,12] In these studies, the opioids sparing effects of esmolol were recognized as a synergistic effect with intraoperative opioids. It may be reasonable to speculate that the opioid-sparing effects of esmolol are likely to be appreciated when used as an adjuvant in a multimodal approach.

While the incidence of PONV was lower in the esmolol group, it did not reduce the time spent in recovery. This is in contrast to the previously described review where patients receiving esmolol had a faster discharge time from the recovery room. Nonetheless, it should be noted that the review included trials comparing esmolol with opioids as well as placebo including vasodilating drugs.[15]

Several theories have been proposed as to the mechanisms of analgesic/opioid sparing and anesthetic effects of esmolol. A decrease in the hepatic metabolism of co-administered opioids secondary to a reduction in the hepatic blood flow; thus, prolonging the action of opioids has been proposed.[22] Another relates to the ability of esmolol to block nociceptive transmission along the different sites in the pain pathway.[23] Furthermore, antinociception has also been linked to a peripheral anti-inflammatory action.[24] Besides, β-blockade related anti-emetic effect has also been proposed.[25] Although data favoring the analgesic, anesthetic, and antiemetic effects of esmolol is available, the current clinical evidence supporting these properties of esmolol is weak.

The risk of perioperative esmolol pertaining to major hemodynamic perturbations and a possibility of awareness due to masking light anesthesia is worth discussing. Two reviews deserve to be mentioned in the context of safety of perioperative esmolol. The first review failed to relate significant bradycardia with esmolol infusion; however, a dose-related hypotension associated with a fixed esmolol-dosing schedule was found.[26] The authors opined that continuous esmolol infusion may be a safer way of administering β-blockers in the perioperative period, and significant hypotension could be avoided by careful titration toward a hemodynamic endpoint.[26] Interestingly, seven[2,3,10,16-19] out of eight trials in our analysis had esmolol titrated to a preselected hemodynamic endpoint, and no major adverse effects were identified. The second review (bolus 0.5–1.0 mg/kg followed by an infusion 100–300 μg/kg/min) showed no significant hypotension or bradycardia with esmolol in noncardiac surgeries.[15] The review highlighted that a negative inotropic effect of esmolol is unlikely to be encountered and that esmolol only causes reversible episodes of hypotension and bradycardia.[15]

Studies have shown that during noxious stimuli, esmolol prevents arousal, and increase in the BIS by blocking β-adrenoreceptors in the reticular formation.[27] This effect can theoretically precipitate awareness by masking the signs of "light anesthesia."[28] BIS was used in two of the three studies that were included in our analysis on volatile anesthetic requirement.[2,3] None of them reported an increase of BIS in the esmolol group. Similarly, no changes in the anesthetic depth were described in studies exploring the anesthetic-sparing effects of esmolol employing BIS.[24] Our review could not identify studies investigating the stress response upon esmolol or opioid exposure. While opioids would blunt the surgical stress response, esmolol may be only effective in blunting the sympathetic response. This may have deleterious effects on the immune system. Future trials may need to explore these differences between esmolol and opioids.

Limitations

The analysis was based on a few studies from single centers. Diverse methodological qualities and heterogeneity between studies were a major limitation. Esmolol dose range was not standardized, and none of the included studies had described a dose-finding pilot study. Only three studies had addressed an adequate sample size calculation.[2,3,10] A low risk of bias could be established in only one included study.[10] A sensitivity or subgroup analysis was limited by the smaller number of trials. Likewise, the inadequate number of trials precluded us in assessing the publication bias. The confounding factors such as age, sex, use of BIS, nitrous oxide, multimodal therapy along with nonstandard anesthetic, antiemetic, and opioid data were further limitations. Ambulatory laparoscopic and arthroscopic surgery performed on a healthier sub-population limits the wider application of our findings. Failure to register our protocol on a registry database and the inclusion of data from an abstract were additional limitations. The included studies span across a few decades; this makes us speculate whether the more liberal discharge criteria (fast-track) used in modern anesthetic practice would change the results if similar trials are attempted now.

A comprehensive literature search without language restriction is one of the strengths of our analysis. Our findings might present a basis for future research investigating esmolol for opioid substitution in the perioperative period.

Conclusion

Meta-analysis of studies comparing esmolol versus opioids indicates that intraoperative esmolol may reduce the incidence of nausea and vomiting. In addition, it increases the volatile anesthetic use. Intraoperative opioid substitution with esmolol has no effect on the PACU discharge time, and it may not have an impact on the early postoperative analgesia. However, the results have to be cautiously interpreted due to the inclusion of few low-quality RCTs and the heterogeneity across studies. Additional well-conducted large trials are needed to establish the role of esmolol on early postoperative recovery.

Acknowledgments

Assistance with the study: we thank Professor M Paech, Shool of Medicine and Pharmacology, The University of Western Australia, A/Prof. John Moran, Discipline of Acute Care Medicine, The University of Adelaide, Dr. John Currie, senior visiting anesthetist of our hospital for their guidances and inputs on this analysis. We thank Mr. T Sullivan, Discipline of Public Health, The University of Adelaide; Dr. A Rea and Dr. K Haskard, Data Analysis Australia for their help in the statistical analysis and S Rockliff of our hospital library in assisting with the literature search.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. White PF, Kehlet H, Neal JM, Schricker T, Carr DB, Carli F; Fast-Track Surgery Study Group. The role of the anesthesiologist in fast-track surgery: From multimodal analgesia to perioperative medical care. Anesth Analg 2007;104:1380-96.
2. Collard V, Mistraletti G, Taqi A, Asenjo JF, Feldman LS, Fried GM, *et al.* Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. Anesth Analg 2007;105:1255-62.
3. Coloma M, Chiu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. Anesth Analg 2001;92:352-7.
4. Bhawna, Bajwa SJ, Lalitha K, Dhar P, Kumar V. Influence of esmolol on requirement of inhalational agent using entropy and assessment of its effect on immediate postoperative pain score. Indian J Anaesth 2012;56:535-41.
5. Chia YY, Chan MH, Ko NH, Liu K. Role of beta-blockade in anaesthesia and postoperative pain management after hysterectomy. Br J Anaesth 2004;93:799-805.
6. Davidson EM, Doursout MF, Szmuk P, Chelly JE. Antinociceptive and cardiovascular properties of esmolol following formalin injection in rats. Can J Anaesth 2001;48:59-64.
7. Hwang WJ, Moon YE, Cho SJ, Lee J. The effect of a continuous infusion of low-dose esmolol on the requirement for remifentanil during laparoscopic gynecologic surgery. J Clin Anesth 2013;25:36-41.
8. Johansen JW, Schneider G, Windsor AM, Sebel PS. Esmolol potentiates reduction of minimum alveolar isoflurane concentration by alfentanil. Anesth Analg 1998;87:671-6.
9. Lee SJ, Lee JN. The effect of perioperative esmolol infusion on the postoperative nausea, vomiting and pain after laparoscopic appendectomy. Korean J Anesthesiol 2010;59:179-84.
10. López-Álvarez S, Mayo-Moldes M, Zaballos M, Iglesias BG, Blanco-Dávila R. Esmolol versus ketamine-remifentanil combination for early postoperative analgesia after laparoscopic cholecystectomy: A randomized controlled trial. Can J Anaesth 2012;59:442-8.
11. Moon YE, Hwang WJ, Koh HJ, Min JY, Lee J. The sparing effect of low-dose esmolol on sevoflurane during laparoscopic gynaecological surgery. J Int Med Res 2011;39:1861-9.
12. Ozturk T, Kaya H, Aran G, Aksun M, Savaci S. Postoperative beneficial effects of esmolol in treated hypertensive patients undergoing laparoscopic cholecystectomy. Br J Anaesth 2008;100:211-4.
13. Orme R, Leslie K, Umranikar A, Ugoni A. Esmolol and anesthetic requirement for loss of responsiveness during propofol anesthesia. Anesth Analg 2002;94:112-6.
14. White PF, Wang B, Tang J, Wender RH, Naruse R, Sloninsky A. The effect of intraoperative use of esmolol and nicardipine on recovery after ambulatory surgery. Anesth Analg 2003;97:1633-8.
15. Landoni G, Turi S, Biondi-Zoccai G, Bignami E, Testa V, Belloni I, *et al.* Esmolol reduces perioperative ischemia in noncardiac surgery: A meta-analysis of randomized controlled studies. J Cardiothorac Vasc Anesth 2010;24:219-29.
16. Lee HY, Kwon WJ, Lee JU. The effects of esmolol, esmolol and nicardipine or remifentanil on mean blood pressure, heart rate and recovery in gynecologic laparoscopic surgery. Korean J Anesthesiol 2008;55:709-15.
17. Lazo OL, Wender RH, Yumul R, Kariger R, Zaentz A, Kaplan M, *et al*. Intraoperative Use of Labetalol and Esmolol vs. Fentanyl for Maintaining Hemodynamic Stability During General Anesthesia for Laparoscopic Surgery: Effect on Recovery and Postoperative Pain. ASA Abstracts, A503; 2012.
18. Bagshaw R, Conahan T, Delling C, Geer R, Levy W, Young M. Esmolol as an anaesthetic adjunct in ambulatory surgery. Ambul Surg 1995;3:13-7.
19. Fuhrman TM, Ewell CL, Pippin WD, Weaver JM. Comparison of the efficacy of esmolol and alfentanil to attenuate the hemodynamic responses to emergence and extubation. J Clin Anesth 1992;4:444-7.
20. Smith I, Van Hemelrijck J, White PF. Efficacy of esmolol versus alfentanil as a supplement to propofol-nitrous oxide anesthesia. Anesth Analg 1991;73:540-6.
21. Apfel CC, Kranke P, Katz MH, Goepfert C, Papenfuss T, Rauch S, *et al.* Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: A randomized controlled trial of factorial design. Br J Anaesth 2002;88:659-68.
22. Takeda S, Masuda R, Kanazawa T, Tomaru T. Esmolol attenuates hepatic blood flow responses during sodium nitroprusside-induced hypotension in dogs. Can J Anaesth 2004;51:348-53.
23. Tanahashi S, Iida H, Dohi S, Oda A, Osawa Y, Yamaguchi S. Comparative effects of ultra-short-acting beta1-blockers on voltage-gated tetrodotoxin-resistant Na+channels in rat sensory neurons. Eur J Anaesthesiol 2009;26:196-200.
24. Kadoi Y, Saito S. Possible indications of beta-blockers in the

perioperative period other than prevention of cardiac ischemia. J Anesth 2010;24:81-95.
25. Gupta YK, Chaudhary G. Effect of antiemetic drugs on decrease in gastric emptying in experimental model of motion sickness in rats. Acta Pharmacol Sin 2003;24:296-300.
26. Yu SK, Tait G, Karkouti K, Wijeysundera D, McCluskey S, Beattie WS. The safety of perioperative esmolol: A systematic review and meta-analysis of randomized controlled trials. Anesth Analg 2011;112:267-81.
27. Menigaux C, Guignard B, Adam F, Sessler DI, Joly V, Chauvin M. Esmolol prevents movement and attenuates the BIS response to orotracheal intubation. Br J Anaesth 2002;89:857-62.
28. Yang H, Fayad A. Are beta-blockers anesthestics? Can J Anaesth 2003;50:627-30.

Appendix 1: Morphine equivalents and volatile anesthetic equivalents conversion table

Morphine equivalents conversion table	
Drug	**Equivalent parental dosage**
Morphine	10 mg
Hydromorphone	1.4 mg
Fentanyl	100 mcg
Alfentanil	25 mcg
Remifentanil	100 mg
Pethidine	100 mg
Sufentanil	20 mg
Volatile anesthetic equivalents conversion table	
Agent	**Minimum alveolar concentration equivalent (%)**
Desflurane	6
Sevoflurane	2.2
Isoflurane	1.15
Halothane	0.75