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The Role of Intraoperative Esmolol vs Ketamine in Laparoscopic Cholecystectomy

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Research Practicum II

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April 16, 2023

Abstract

As the understanding of opioid dependence mechanisms and origins in the adult population continues to evolve in the United States, so does the pursuit of alternative avenues for analgesia. Many opioid substance-use disorder patients can trace the origins of their dependence to routine prescription and administration of opioids during surgical procedures (Bohringer et al., 2020). One such procedure where opioids are frequently utilized for intraoperative and postoperative analgesia is laparoscopic cholecystectomy. Incidence of gall bladder disease is closely related to obesity (Hines & Marschall, 2018). Gallstone disease continues to be a common and costly health problem affecting 10 to 20% of the US adult populations (NIH, 2023). The definitive treatment for acute cholecystitis is removal of the gall bladder commonly performed utilizing the laparoscopic technique (Hines & Marschall, 2018).

Does the use of intraoperative esmolol versus ketamine infusion in adult patients undergoing laparoscopic cholecystectomy surgery improve postoperative pain? This literature review sought to better understand the role of two non-opioid adjuncts, esmolol and ketamine, in postoperative pain for adults undergoing laparoscopic cholecystectomy. When measured in terms of pain intensity and opioid consumption postoperative nociception was improved with intraoperative esmolol and ketamine compared opioids and other non-opioid adjuncts.

Keywords: esmolol, ketamine, postoperative pain, opioid consumption, laparoscopic, cholecystectomy

The Role of Intraoperative Esmolol vs Ketamine in Laparoscopic Cholecystectomy

The understanding of opioid dependence mechanisms and origins in the adult population continue to evolve in the United States. Many opioid substance-use disorder patients can trace the origins of their dependence to routine administration and prescription of opioids during surgical procedures (Bohringer et al., 2020). As a result of the opioid epidemic the pursuit of alternative avenues for analgesia required during the perioperative and postoperative periods are evolving as well. Opioids are the most common medications used to treat perioperative and postoperative pain. Nonopioid adjuncts can provide effective analgesia without the side effects of opioids (Benzon et al., 2018). Given the United States' opioid epidemic, opioid stewardship i.e., the judicious use of opioids combined with multimodal nonopioid adjuncts is an anesthetic technique at the forefront for controlling perioperative nociception, reducing postoperative opioid consumption, and postoperative pain intensity. Laparoscopic cholecystectomy is a routine surgical procedure where opioids are frequently utilized for intraoperative and postoperative analgesia (Nagelhout & Elisha, 2018).

In the United States the incidence of acute postoperative pain is as high as 80% in surgical patients (Gan et al., 2014). The perception and chronicity of postoperative pain is dependent upon several factors including, but not limited to psychological, emotional, social, genetic, surgical, anesthetic factors, and prior experiences of post-surgical pain (Moro et al., 2017). Even though postoperative pain in cholecystectomy is reduced with the laparoscopic technique, patients can still experience postoperative pain (Lopez-Alvarez et al., 2012). Lopez-Alvarez et al. (2012) asserts that a multiple modal technique to treat postoperative pain experienced by laparoscopic cholecystectomy patients can lessen postoperative narcotic requirements and facilitate early recovery.

Two such nonopioid adjuncts are ketamine and esmolol. This literature review focuses on determining the role of esmolol, a newer nonopioid adjunct, and ketamine a well-known nonopioid adjunct in laparoscopic cholecystectomy in postoperative pain intensity and opioid consumption.

Background

Cholelithiasis

Gallstones form from cholesterol or bilirubin into hard, pebble-like stones in the gall bladder (NIH, 2023). Small stones can pass through the biliary tract and be eliminated without eliciting any symptoms. Larger stones or a collection of smaller stones may not pass without causing pain and discomfort- if they pass at all. When these stones block the bile ducts of the biliary tract, patients exhibit sudden right upper quadrant pain and require removal of the stones or the gall bladder completely in a surgical procedure called a cholecystectomy. Complications from stones blocking the bile ducts include inflammation or damage to the gallbladder, bile ducts, and liver. Additional complications include infection, pancreatitis, and damage to the bile ducts and liver.

According to Azeem et al. (2023) in the United States over 20 million people develop cholelithiasis and of those 10-15% will become symptomatic. Laparoscopic cholecystectomy is a common and routine surgery where nonopioid adjuncts can be effective in lowering opioid requirements and postoperative pain. Roughly 90% of elective cholecystectomies or approximately >750,000 are performed laparoscopically in the United States annually (Al Ain Atiff et al., 2022).

Identifiable risk factors for developing gall bladder disease include obesity, rapid weight loss as seen following weight loss surgery, family history, female gender,

hypercholesterolemia (especially in American Indians and Mexican Americans), hyperlipidemia, Crohn's disease, metabolic syndrome, diabetes, and insulin resistance (NIH, 2023).

Obesity

The Centers for Disease Control and Prevention (CDC) defines adult obesity as a body mass index (BMI) of $\geq 30\text{kg/m}^2$. The prevalence of adult obesity from 1999 to 2017 in the United States has increased from 30.5% to 41.9% of the population (CDC, 2023). The prevalence of severe obesity defined as a BMI of $\geq 40\text{kg/m}^2$, has increased from 4.2% to 9.7% of the population in the same time frame (CDC, 2023). The incidence of gall bladder disease is closely related to obesity (Hines & Marschall, 2018). Gallstone disease continues to be a common and costly health problem effecting 10 to 20% of the United States adult population (NIH, 2023). Obese patients have higher levels of serum cholesterol compared to nonobese patients (NIH, 2023). The risk of developing gall stones further increases in obese women who have an android or truncal distribution of fat (NIH, 2023).

Pain

According to Nagelhout & Elisha (2018) nociception is a response to specific noxious stimuli that is classified as either somatic or visceral. Somatic pain involves several processes including, transduction, transmission, perception, and modulation. Peripheral nociceptors transmit noxious stimuli via myelinated and non-myelinated nerve fibers to the dorsal horn of the spinal cord. Fast A-delta fibers ($A\delta$) are myelinated primary afferent neurons that conduct thermal and mechanical pain that is fast and sharp in nature. Slower nonmyelinated C fibers or polymodal fibers, respond to mechanical, thermal, or chemical stimuli that are transmitted to the dorsal horn of the spinal and produces a dull, throbbing, and aching pain sensation. The wide dynamic range (WDR) neurons are stimulated by both $A\delta$ and C fibers. Non-nociceptive or

neuropathic pain is associated with central nervous system dysfunction. Inflammatory pain is a nociceptive pathway that does not involve neural injury and mediated through multiple factors (Nagelhout & Elisha, 2018).

Chemical, mechanical, or thermal injury causes tissue to release multiple chemical mediators and neurotransmitters are released (Nagelhout & Elisha, 2018). These substances include substance P, glutamate, bradykinin, histamine, serotonin, prostaglandins, cytokines, and calcitonin gene-related peptide (CGRP) (Nagelhout & Elisha, 2018).

Substance P, a neurokinin, is released from peripheral afferent nociceptor C fibers that stimulates the g-coupled Neurokinin-1 receptors (NK-1) (Nagelhout & Elisha, 2018). Stimulation of the NK-1 receptors cause vasodilation, mast cell degranulation, and sensitization of stimulated sensory nerves (Nagelhout & Elisha, 2018).

Tachykinins are highly excitable neuropeptides that play a central role in nociception (Garcia-Recio & Gascon, 2015). Neurokinin-1 is an important neuropeptide neurotransmitter that is a member of the tachykinin family (Garcia-Recio & Gascon, 2015). NK-1 is widely accepted as a mediator in spinal cord sensitization and hyperalgesia (Rivat et al., 2009). The main receptor in the tachykinin family is a g-coupled protein called NK-1, which has a high affinity for substance P (Garcia-Recio & Gascon, 2015). NK-1 positive neurons project into the spinothalamic and spinoreticular tracts (Rivat et al., 2009).

In chronic or neuropathic pain there is increasing evidence that the NK-1 pathway is integral to its transmission and processing by increasing the excitability of dorsal root ganglion (DRG) neurons (Chen et al., 2016). Interestingly, in post myocardial infarction (MI) patients, the NK-1 pathway is interrupted by esmolol (Wang et al., 2013). The interruption of the NK-1

pathway has been theorized to be esmolol's mechanism of action preventing post MI dysrhythmias (Wang et al., 2013).

Opioid Epidemic

According to the CDC, drug overdose deaths remain the leading cause of injury related deaths in the United States (CDC, 2023). From the years 1999 to 2017 the number of deaths related to opioid overdose in the United States had a fourfold increase (Scholzen et al., 2019). During those years the fourfold increase amounted to approximately 47,000 deaths in the United States (Scholzen et al., 2019). In recent years, drug overdose deaths have been increasingly caused by fentanyl, cocaine, and methamphetamines (CDC, 2023). Individual states have worked through public information campaigns, education, and changes in prescriber practices to either arrest or decrease drug overdose deaths. The exception to this nationwide trend is Arizona, which has seen a significant increase in deaths related to drug overdose of 26.9% (CDC, 2023).

Starting in 2006, there was a steady increase in prescription opioid dispensing across the United States that peaked in 2012, when the dispensing rate for opioids was 81.3 prescriptions per 100 persons (CDC, 2023). In the subsequent years, the number of opioid prescriptions has steadily decreased to the current national average of 43.3 prescriptions per 100 people (CDC, 2023). However, in 3.6% of United States' counties the opioid prescription rate is 9 times higher than the current national average. Cicero et al. (2014) conducted a survey of urban injection drug users who were seeking treatment for heroin addiction. Cicero et al. (2014) found that 65% of those abusing opioids during the 2000's, their source for nonmedical opioids was family, friends, and personal opioid prescriptions. Prior to the 2000's the source of heroin addiction was primarily from heroin and not opioid prescriptions (Cicero et al., 2014). Alam et al. (2012) conducted a retrospective cohort study on postsurgical long term analgesic use in

391,139 opioid naïve patients who underwent low-risk surgery. Alam et al. (2012) found that of patients who received opioid prescriptions within 7 days of surgery, 44% were more like to become long term opioid users within 1 year of surgery as compared to those who did not.

Anesthesia providers are uniquely positioned to collaborate across multiple health care disciplines and bridge the gap between acute inpatient and after discharge pain management of surgical patients (Hah et al., 2017). By providing anesthetic techniques such as neuraxial and regional anesthesia, as well as multimodal medications, anesthesia providers can decrease postoperative opioid need or consumption (Hah et al., 2017).

Opioid Free Anesthesia

Independent of opioids prescribed by non-anesthesia health care providers for the management of non-surgical and postoperative surgical pain experienced by patients at home, the anesthesia provider's use of opioids in treating acute pain is limited to the perioperative and immediate postoperative phase. The traditional method of treating perioperative and postoperative pain by anesthesia providers has been opioids (Gupta et al., 2020). Opioids are routinely chosen by anesthetic providers, not only for their ability to control nociception, but to optimize intraoperative hemodynamics. Additionally, opioid use during perioperative and postoperative phase has been attributed to increased postoperative nausea vomiting, constipation, and opioid-induced respiratory depression (OIRD) (Gupta et al., 2020).

Despite efforts to eradicate the opioid epidemic, barriers to the implementation of opioid free anesthetics persist (Morrow et al., 2022). Barriers to opioid free anesthesia (OFA) technique are multifactorial. One such barrier among anesthesia providers is that OFA has no accepted definition, i.e., most providers who say they practice OFA, do in fact administer parenteral opioids as part of their anesthetic plans (Gupta et al., 2020). Gupta et al. (2020) asserts that most

OFA providers limit the amounts of parenteral opioids they give their patients and practice a multimodal approach to postoperative analgesia. Additionally, Gupta et al. (2020) asserts that most current evidence supports an opioid sparing not an opioid free anesthetic. However, OFA is not appropriate for every surgery or patient. Introducing OFA may mean changing established clinical practice which can be significantly behind current evidence-based practices and research (Carcamo-Cavazos & Cannesson, 2022).

Morrow et al. (2022) identified additional barriers to OFA implementation among Certified Registered Nurse Anesthesiologists (CRNA) surveyed in Arizona- currently the state with the highest deaths related to opioid overdose. The survey included the age, years of experience, experience with peripheral nerve blocks, level of education, and gender of the CRNA. In Morrow et al. (2022)'s survey, CRNAs cited multiple barriers to implementing OFA techniques that were independent of the CRNAs' demographics. These barriers included institutional culture, availability of OFA agents, and availability of equipment (i.e., ultrasound machines or syringe pumps) (Morrow et al., 2022).

The benefits of a multimodal approach to analgesia include fast track surgery, decreased hospital stays, promotion of early enteral nutrition, as well as increased early postoperative mobilization (Bhardwaj et al., 2019). Contrary to opioids, OFA or opioid sparing anesthesia reduces the risk of OIRD, which is of significant concern in obese patients who inherently have decreased functional residual capacity (FRC), restrictive lung disease secondary to their body habitus, and increased risk of obstructive sleep apnea (OSA) that is most often undiagnosed (Bhardwaj et al., 2019). Non-opioid adjuncts such as dexmedetomidine and ketamine, can effectively treat pain and preserve respiratory drive, which is of particular importance in obese patients (Bohringer et al, 2020).

Esmolol and Ketamine as Nonopioid Adjuncts

According to Nagelhout & Elisha (2018) the N-methyl- d -aspartate (NMDA) glutamate receptor is a ligand-gated voltage dependent ion channel mediated by calcium and sodium ions. The amino acid, L-glutamate, is integral to the excitation of the central nervous system. It acts on the NMDA receptor by opening it, thus allowing a rapid influx of calcium, potassium, and sodium into the cell. L-glutamate is released not only from the CNS, but from A δ and C fibers. L-glutamate's effects on A δ and C fibers produce instant sharp and fast pain. The influx of positive ions into the cell caused by L-glutamate, effectively depolarizes the postsynaptic membrane and initiates an action potential allowing the cortical regions of the brain to interpret afferent pain signals (Naghelout & Elisha, 2018).

Ketamine is a noncompetitive NMDA glutamate receptor and sodium channel antagonist that blocks postsynaptic membrane depolarization (Naghelout & Elisha, 2018). The resulting selective depressant effects in the medial thalamic nuclei from NMDA antagonism inhibits the afferent pain signals to the thalamus and cortex (Naghelout & Elisha, 2018). Thus, the afferent pain signal is transmitted to the central nervous system, but central sensitization does not occur (Naghelout & Elisha, 2018). Noxious stimuli transmission from the spinal cord to the brain may also be prevented by ketamine's ability to block excitatory signaling of neurons in the dorsal horn (Naghelout & Elisha, 2018). Ketamine not only stops the interpretation of pain signals, but the transmission of pain signal from the spinal cord. Ketamine's effects are not limited to the CNS, its inhibitory effect on the gene expression of cytokines, tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), may produce anti-inflammatory and anti-hyperalgesia effects.

Ketamine has many of the analgesic properties of opioids without their adverse side effects (Benzon et al., 2018). Racemic ketamine has 2 stereoisomers, R- and S-, a half-life of 80-

180 minutes. Norketamine, racemic ketamine's metabolite, is 1/3 as potent and has a longer half-life than its parent compound (Benzon et al., 2018). While ketamine does not suppress respiratory or cardiac functions it is not without its drawbacks. These drawbacks include metabolite accumulation, psychomimetic effects, and postoperative malaise (Benzon et al., 2018). For ketamine to express its analgesic effects a plasma concentration of 100-150ng/mL must be achieved (Benzon et al., 2018). Ketamine crosses the blood brain barrier quickly, its distribution is not dose dependent, it is quickly redistributed from central to peripheral compartments, and is only 12% protein bound (Nagelhout & Elisha, 2018).

Given its pharmacokinetics and dynamics the most effective method of administering ketamine perioperatively and producing postoperative reduction in opioid consumption and pain intensity- is via an intravenous (IV) bolus with a continuous infusion started prior to incision rather than bolus dosing (Benzon et al., 2018). Low dose ketamine infusions or subanesthetic doses of <0.5 mg/kg it did not elicit the psychomimetic effects of ketamine such as nightmares, sleep disturbances, hallucinations, or worsen psychiatric disorders (Benzon et al., 2018). Additionally, at subanesthetic doses, ketamine is noted to elicit the forementioned adverse side effects (Benzon et al., 2018). Ketamine's ability to control nociception in the perioperative setting, as well as improve postoperative pain intensity and opioid consumption has been effective in a variety of surgeries including spine, pelvic, and abdominal.

Esmolol is a selective beta-1 receptor antagonist with an onset of 2 minutes and short elimination half-life of 9 minutes secondary to metabolism by plasma esterases (Nagelhout, 2018). Esmolol is easily titratable and is commonly used to treat intraoperative tachyarrhythmias (Benzon et al., 2018). Traditionally, esmolol has been used to blunt the adrenergic response to direct laryngoscopy, extubation, and surgical stimulation (Benzon et al., 2018). However, the

effects of intraoperative esmolol on postoperative pain intensity and opioid consumption are increasingly being studied (Haghighi et al., 2015).

While esmolol has no proven mechanisms of action in controlling nociception there are several theories (Benzon et al., 2018). Bahr & Williams (2018) cites several theoretical antinociceptive mechanisms of beta antagonists: I) is accomplished by blocking the β -adrenergic receptors in brainstem thus reducing neuronal inflow to the CNS and consequently modulating the stress response to noxious stimuli by preventing the release of norepinephrine and neuropeptide Y from postganglionic sympathetic neurons; II) blocking β -adrenergic receptors in the hippocampus preventing the release of norepinephrine during stress; III) by changing the pharmacokinetics of opioids of short acting opioids.

In rat studies the reduction of pain by beta antagonists like, esmolol, were secondary to their ability to reduce neuronal responses to stimulation in the cingulate cortex (Haghighi et al., 2015). As previously stated, the NK-1 pathway has been identified as not only a pathway of chronic pain and opioid induced hyperalgesia, but for post myocardial infarction (MI) dysrhythmias. Esmolol, binds to the g-coupled NK-1 receptor and blocks substance P from binding to and stimulating it (Wang et al., 2013). Blocking the NK-1 receptor from stimulation by substance P presents a potential explanation for esmolol's mechanism of action in treating perioperative nociception (Wang et al., 2013).

Literature Review

Methods

A literature search was performed on the following data bases: Google scholar, CINAHL, Cochrane Library, National Institutes of Health, and PubMed. Studies published within the last 5 years that met strict criteria were selected. However, additional studies published within the past

10 years that met the same strict criteria were selected for this literature review. The literature search was performed using a key word search for both ketamine and esmolol. Other key words included, “laparoscopic cholecystectomy”, “postoperative pain”, “laparoscopic”, “adjunct”, and “safety”.

Randomized control trials (RCT’s), prospective RCT’s, double blinded, systemic reviews of RCT’s, and meta-analysis of RCT’s were included. Quasi-experimental, single blind studies, case studies, and pilot studies were excluded. Thirty-one studies were considered for this literature review, 7 studies were excluded secondary to publish date greater than ten years and lower strength levels of evidence.

In all the studies included in this literature review participants had an American Society of Anesthesiologists (ASA) physical status classification of I or II. Except for Watts et al. (2017), participants with an ASA physical status classification of greater than II were excluded from the studies in this literature review. Watts et al. (2017) did not delineate any differences between ASA physical status classification postoperative pain intensity and opioid consumption and was therefore not considered a source of heterogeneity. Thus, different ASA physical status was not a source of heterogeneity in any of the studies in this literature review. Age ranges for the studies varied between 18 and 97 years of age. All the studies in this literature review excluded pediatric patients defined as an age <18 years old. The group demographics within each study had no significant differences. Anesthetic plans in each study were kept standard across the study groups, except for study drugs. Statistical significance for all studies was determined to be a p value <0.05.

In this literature review, four studies Watts et al. (2017), Duarte de Moraes et al. (2020), Haghghi et al. (2015), and Mahrose & Elgharabawy (2020) compared intraoperative esmolol

infusion to placebo. Bajracharya et al. (2019) and Dogan et al. (2016) compared intraoperative esmolol infusions versus lidocaine infusions. Gelineau et al (2018) was a metanalysis that compared intraoperative esmolol infusions to intraoperative opioid. Lee & Lee (2010), Lopez-Alvarez et al. (2012), and Lee et al. (2014) compared intraoperative esmolol, ketamine, and remifentanil infusions. Ji et al. (2022) compared intraoperative esmolol versus ramonestron. In this literature review, Abdelfatah & Amin (2021) was the only study that compared intraoperative esmolol to trans-abdominal plane block (TAP block). Ye et al. (2017), Wang et al. (2021), and Zhang et al. (2022) were three studies that compared intraoperative ketamine versus placebo. Mercanoglu et al. (2022) compared the intraoperative use ketamine to another non-opioid adjunct, dexmedetomidine. Moro et al. (2017) is the only study included in this literature review that assessed the efficacy different intraoperative ketamine doses. Twelve studies in this literature review compared either intraoperative esmolol or ketamine in patients undergoing laparoscopic cholecystectomy specifically: Mercanoglu et al. (2022), Moro et al. (2017), Ye et al. (2017), Wang et al. (2021), Zhu et al. (2018), Zhang et al. (2022), Abdelfatah & Amin (2021), Bajracharya et al. (2019), Dogan et al. (2016), Gelineau et al. (2018), Ji et al. (2022), and Lopez-Alvarez et al. (2012). Bajracharya et al. (2019) was the only study that only included female participants undergoing laparoscopic cholecystectomy. Dose response curves were not specifically studied in any of the studies included in this literature review, except in Chen et al, (2020).

The literature search revealed common outcomes across all 24 papers included in this literature review and are as follows: intensity of postoperative pain, incidence of postoperative nausea vomiting, intraoperative hemodynamics, opioid consumption, and recovery to discharge

times. This literature review focuses on outcomes related to postoperative pain: postoperative pain intensity and opioid consumption.

Esmolol and Postoperative Opioid Consumption

Abdelfatah & Amin (2021) performed a prospective randomized controlled trial (RCT) to study the efficacy of intraoperative esmolol as an adjunct to a TAP block in patients undergoing laparoscopic cholecystectomy. Participants who only received a TAP block were considered the control. Patients in group E received esmolol as a loading dose of 0.5 mg/kg, followed by a continuous infusion of 0.05 mg/kg/min. Patients in group T received normal saline as a loading dose followed by a continuous infusion of normal saline of equivalent volumes to the esmolol received in group E. To limit bias, Abdelfatah & Amin (2021) utilized a double-blind method, where patients were randomly assigned to groups utilizing a computer-generated digital table. Investigators and patients were unaware of group assignments, infusion volumes were the same (30ml's) for either TAP block or esmolol group. Postoperative Visual Analogue Scale (VAS) pain scores were collected by an investigator blinded to the study. Morphine consumption was lower in group E, 5.83 mg (+/- 2.87 mg) compared to group T, 7.5mg (+/- 3.65 mg). However, these results were determined not to be statistically significant as the $p=0.204$ (Abdelfatah & Amin, 2021).

Bajracharya et al. (2019) was a prospective RCT that studied the efficacy of esmolol versus lidocaine use in female patients who underwent laparoscopic cholecystectomy. Female patients were 18-60 years of age. Bajracharya et al. (2019) used a double-blind method and a computer-generated random number table to assign patients to each group. Additionally, in Bajracharya et al. (2019) group assignments and case numbers were delivered using the sealed envelope method. Thus, participants and investigators were kept blinded. The intraoperative

anesthesiologists were not involved in postoperative data collection. However, a placebo group was not included as Bajracharya et al. (2019) asserted that the lidocaine group was the control. Both groups received standard IV loading doses and infusions of each respective drug, esmolol or lidocaine. Bajracharya et al. (2019) determined there was no statistical significance in opioid consumption as measured by morphine equivalents between either the esmolol or lidocaine groups. The median morphine consumption in the esmolol group was 1 mg (range, 0-1.5 mg) as compared to 1.5 mg (range, 1-2 mg) in the lidocaine group ($p=0.27$; Bajracharya et al., 2019).

Dogan et al. (2016) was a RCT that studied intraoperative esmolol versus lidocaine infusions in patients between 18- 65 years old who underwent a laparoscopic cholecystectomy. Participants were randomized into two groups, group L (lidocaine) and group E (esmolol), by sealed envelope method. Group L received a total lidocaine dose of 1.5 mg/kg/minute during the maintenance phase and a total dose of 2 mg/kg/hour beginning at 3 minutes prior to induction. Group E received a total esmolol dose of 1 mg/kg/minute during the maintenance phase and 15 mcg/kg/minute beginning at 3 minutes prior to induction. Both esmolol and lidocaine infusions were terminated immediately after extubation. Postoperative pain control was achieved using a fentanyl patient-controlled analgesia (PCA) with standard dosing and time intervals for both groups. Additional rescue analgesia of 75 mg intramuscular (IM) diclofenac, a nonsteroidal anti-inflammatory drug (NSAID), every 12 hours for VAS pain scores ≥ 4 . Opioid consumption was measured based on fentanyl consumption from a postoperative fentanyl PCA (Dogan et al., 2016).

Dogan et al. (2016) determined that opioid consumption in the esmolol group was 82.50 mcg (+/-28.36 mcg) and lidocaine group 94.66 mcg (+/-45.08 mcg). These results were not statistically significant, as p was 0.298. However, group L (lidocaine) was noted to require less

additional doses of fentanyl above the preset fentanyl PCA as compared to group E (esmolol), 2 patients (6.7%) and 11 patients (36.7%), respectively ($p < 0.005$). Despite patients in group L requiring less additional doses of fentanyl there was no statistical difference between either group in terms of number of demand-attempts from fentanyl PCA (Dogan et al., 2016).

Duarte de Morais et al. (2020) was a prospective comparative RCT study that compared the efficacy of esmolol to placebo on postoperative pain intensity. Patients included in this study underwent gastroplasty and were between the ages of 18-50 years old. This study utilized a double-blind method to limit bias. Duarte de Morais et al. (2020) determined that participants in the esmolol group consumed less total morphine, 7 mg (+/- 4.4 mg) as compared to placebo group, 13 mg (+/- 5.7 mg) in the 24-hour postoperative period ($p = 0.002$, no CI reported; Duarte De Morais et al., 2020).

Gelineau et al. (2018)'s large systematic review included a meta-analysis and meta-regression of 23 RCT studies. In this study there were 1339 participants between the ages of 23-97 years of age. It specifically looked at the effects of esmolol versus opioid on intraoperative opioid requirements and postoperative pain outcomes in laparoscopic gynecologic surgeries, appendectomy, cholecystectomy, as well as orthopedic, lower abdominal procedures abdominal (including open total abdominal hysterectomy), and septorhinoplasty. The control groups received either intraoperative crystalloid or opioids. The cumulative intraoperative and PACU opioid consumption was measured by standard mean difference (SMD) (Gelineau et al., 2018).

Gelineau et al. (2018) performed a meta-regression to address the high heterogeneity noted in its systematic review ($I^2 = 95.2\%$). The meta-regression attributed the high heterogeneity to the crystalloid and opioid control groups. Regardless of the type of control group, patients who received intraoperative esmolol required less postoperative morphine. Gelineau et al. (2018)

found that in 659 participants who received intraoperative esmolol their cumulative Post Anesthesia Care Unit (PACU) opioid consumption was lower than in participants who did not receive intraoperative esmolol. Postoperative morphine consumption in the esmolol compared to crystalloid control groups, SMD -1.23 ($p \leq 0.001$; CI=95%). Postoperative morphine consumption in the esmolol compared to opioid control groups, SMD -1.18 ($p = 0.048$, CI=95%; Gelineau et al., 2018).

Haghighi et al. (2015) conducted a double-blind RCT that studied postoperative pain scores in participants who received intraoperative esmolol infusions versus placebo. The study had 82 participants between ages of 20-60 years old that were randomly allotted into two groups, A and B. Group A received intraoperative infusion of esmolol and group B received a placebo infusion of equal volume. Pethidine (meperidine) was used to treat postoperative pain in both groups. Postoperative pain was scored using a Visual analogue scale (VAS). Haghighi et al. (2015) determined that the participants in group A (esmolol) consumed significantly less pethidine as compared to group B (placebo), 73.14 mg (+/- 36.38 mg) to 93.89 mg (+/- 25.21 mg) respectively ($p=0.004$; Haghighi et al., 2015).

Ji et al. (2022) conducted a double-blind RCT that studied esmolol's effect on the consumption of ketorolac and ramosetron (antiemetic) in patients between ages 20-50 years old who underwent laparoscopic cholecystectomy. Participants in were randomly assigned using a computerized random sequence generator program into three groups R, E, and E+R. Group R received intraoperative ramosetron only. Group E received intraoperative esmolol infusion only. Group E+R received intraoperative esmolol infusion and ramosetron. Fentanyl consumption was not significantly different between the groups, 65.46 mcg, 66.50 mcg, 67.80 mcg in group R, E, and E+R respectively ($p=0.69$). Interestingly, within the first 30 minutes of the postoperative

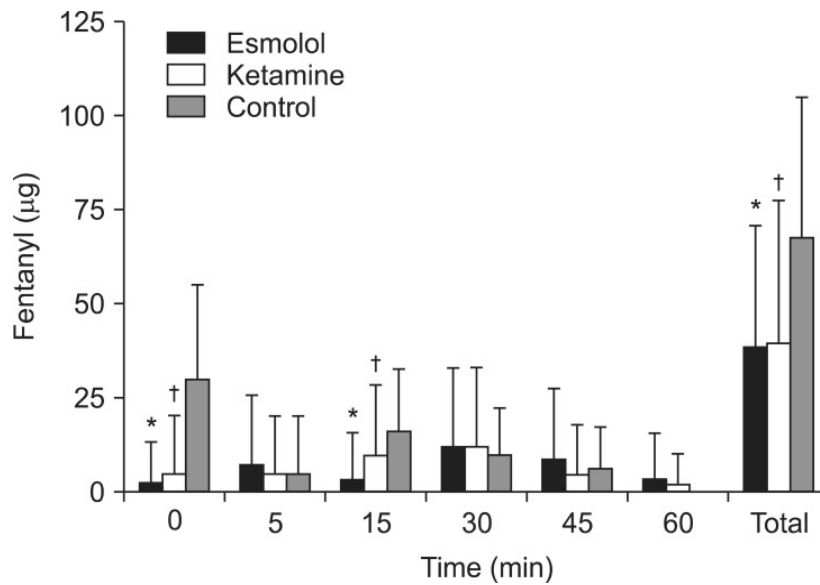
period ketorolac consumption was less in the groups E, 39 mg, and E+R, 38.4 mg, as compared to group R, 54.6 mg ($p<0.001$; Ji et al.2022).

Lee et al. (2014) conducted a prospective RCT that compared the efficacy of intraoperative esmolol and ketamine in patients between the ages of 20-70 years of age that underwent laparoscopic cholecystectomy. Sixty patients were allotted into three groups ketamine, esmolol, and control group. Patients in all three groups received an intraoperative infusion of remifentanyl at a standard dose. The esmolol group received an intraoperative bolus dose followed by an infusion of esmolol. The ketamine group received a bolus dose followed by a continuous infusion of ketamine. The control group received a placebo of normal saline of equivalent volume to the study drugs in addition to a remifentanyl infusion. The anesthesia providers were blinded to the intraoperative study drugs. Postoperative pain was measured from arrival to the recovery unit to 1-hour at 15-minute intervals. Postoperative pain was measured using a VAS (0-10) and fentanyl was given when VAS pain scores were >4 . Fentanyl consumption was reported in terms of μg as a mean \pm SD at each 15-minute postoperative time interval and as a total for the first postoperative hour (Lee et al., 2014).

Lee at al. (2014) determined that at the postoperative 5- and 15-minute intervals both the esmolol and ketamine groups required less fentanyl compared to the control group ($p<0.05$). The esmolol and ketamine groups consumed cumulatively less fentanyl for the first postoperative hour as compared to the control group ($p<0.05$). Additionally, between the ketamine and esmolol group there was no statistically significant difference noted in the total amount of fentanyl consumed during the postoperative period ($p>0.05$; see Figure 1; Lee et al., 2014).

Figure 1

Postoperative Fentanyl Consumption



Note. Figure adapted from “Comparison of effects of intraoperative esmolol and ketamine infusion on acute postoperative pain after remifentanyl-based anesthesia in patients undergoing laparoscopic cholecystectomy,” by Lee, M.H., Chung, M.H., Han, C.S., Lee, J.H., Choi, Y.R., Choi, E.M., Lim, H.K., Cha, Y.D. (2014). *Korean Journal of Anesthesiol*, 66(3), 222-229. <https://dx.doi.org/104097/kjae.2014.66.3.222>

A RCT by, Lee & Lee (2010) studied esmolol’s effect on the severity of PONV, postoperative pain, perioperative remifentanyl use, hospital stay length, and perioperative hemodynamics in patients between ages of 18-45 years old. The patients received total intravenous anesthesia (TIVA) in laparoscopic appendectomy. Sixty participants were randomized into 2 groups, E and C. Group E received perioperative esmolol infusion and group C (control) received no perioperative esmolol. TIVA included propofol and remifentanyl infusions for both groups, which was stopped after skin suturing was completed. Group E received an esmolol loading dose of 1 mg/kg followed by an infusion of 10 mcg/kg/min. Additionally, group E was given a bolus esmolol to 1 mg/kg immediately prior to and continued until after extubation. Group C received an equivalent volume of normal saline to the esmolol infusion given in group E. Diclofenac (NSAID) was utilized for postoperative pain management. During the postoperative and recovery phase the total amount of diclofenac consumed was less

in group E as compared to group C, 120mg (+/-30 mg) and 180 mg (+/-75 mg) respectively ($p < 0.05$; Lee & Lee, 2010).

Lopez-Alvarez et al. (2012) used a double-blind RCT to study the cumulative consumption of morphine in the PACU period in patients who received intraoperative esmolol infusions compared to those who received intraoperative ketamine and remifentanyl. Patients in the study were between 18-85 years old and underwent laparoscopic cholecystectomy. The participants were randomly allocated into two groups, E and R+K. Group E patients received intraoperative esmolol infusion. Group R+K patients received intraoperative remifentanyl infusion and ketamine. Lopez-Alvarez et al. (2012) reported median morphine consumption in the PACU. The median morphine consumption in group E was 0 mg compared to 5 mg in group R-K. This result was determined to be statistically significant ($p < 0.001$). Additionally, in group E only 23% (7 of 30 participants) required morphine versus 83% (25 of 30) participants in group R-K. The 60% difference in participants who required morphine had a 95% confidence interval (CI) (no p was reported; Lopez-Alvarez et al., 2012).

The cause of the higher percentage of patients requiring morphine during the postoperative phase in the remifentanyl-ketamine group was not addressed in Lopez-Alvarez et al. (2012). Whether or not secondary opioid induced hyperalgesia caused by remifentanyl influenced ketamine's lack of efficacy on postoperative morphine consumption noted in this study could not be determined (Nagelhout & Elisha, 2018). Benzon et al. (2018) asserted that intraoperative remifentanyl infusions had no beneficial effect on ketamine's analgesia effect. Additionally, the intraoperative use of ketamine was further supported by a review of 4700 patients undergoing upper abdominal, thoracic, and major orthopedic surgeries that demonstrated

a decrease in morphine consumption and postoperative pain intensity when intraoperative ketamine was used independent of remifentanyl (Benzon et al., 2018).

Mahrose & Elgharabawy (2020) used a double-blinded prospective RCT study design that compared intraoperative esmolol infusions versus placebo in postoperative analgesia. Sixty participants between the ages of 18-59 years old with a BMI of 40-50 kg/m², who underwent elective abdominal laparoscopic bariatric surgeries were included in this study. Participants were allocated into two groups using computer-generated random numbers. Group E received intraoperative esmolol infusion and group N received an equivalent volume of normal saline as an intraoperative infusion. Values were expressed as mean (+/- standard deviation or SD) and percentage. Mahrose & Elgharabawy (2020) found that the number of patients who required rescue analgesics in the first postoperative 24-hours were less in the esmolol group compared to control group, 13.3% (4 of 30) and 43.3% (13 of 30) respectively ($p=0.0219$, no CI reported; Mahrose & Elgharabawy, 2020).

Watts et al. (2017) systematic literature review and meta-analysis measured the cumulative postoperative opioid consumption from PACU to postoperative day three in patients who received intraoperative esmolol infusions versus a placebo of equivalent volume. Opioid doses were reported as morphine equivalents. The intraoperative esmolol group's opioid consumption was reduced by a mean of 5.1 mg ($p<0.001$, CI 95%). Postoperative morphine dosing had significant heterogeneity ($I^2=96.9%$) which suggested that different esmolol infusion doses were a possible contributing factor. However, a further meta-regression analysis showed residual heterogeneity was 94.8%, suggesting that different esmolol infusion rates did not contribute to postoperative morphine dosing heterogeneity. Regardless of the intraoperative esmolol infusion dose, the overall need for rescue analgesia as measured in morphine

equivalents, was less in participants who received esmolol versus placebo by 69% ($p=0.0001$, $I^2=0.0\%$, CI 95%; Watts et al., 2017).

Esmolol and Postoperative Pain Intensity

Abdelfatah & Amin (2021) study measured intraoperative esmolol infusion's effect on postoperative pain intensity at rest and with activity versus TAP block. Postop pain intensity was measured using a VAS from 0-5. The VAS pain scores were reported as a mean and SD. The postoperative phase was defined as arrival to PACU, PACU hour 1, and PACU hour 2.

Postoperative pain scores were assessed on arrival to the PACU and then at the subsequent one and two hours. Resting VAS pain scores at the PACU hour 1 interval were lower in group E (esmolol), mean 0.63 and SD 0.61, than in group T (TAP block), mean 1.17 and SD 1.23. These results were found to be statistically significant where the p was 0.038. VAS scores with activity were lower at PACU hour 1 in group E (esmolol), mean 0.97 and SD 0.85, compared to group T (TAP block), mean 1.7 and SD 1.64 ($p=0.034$). Resting VAS pain scores at the 2-hour PACU interval were lower in group E (esmolol), mean 1.3 and SD 0.84, than group T (TAP block), mean 1.86 and SD 1.04 ($p=0.023$; Abdelfatah & Amin, 2021).

Bajracharya et al. (2019) evaluated postoperative dynamic and rest pain intensity using in female patients who received either intraoperative infusion of esmolol or lidocaine. Pain was assessed using VAS. VAS pain scores were evaluated on arrival to PACU followed by every 5-minutes up to 1 hour during the postoperative phase until a goal VAS pain score ≤ 3 . Pain intensity continued to be evaluated for an additional 24 hours in a surgical unit at 2, 6, 12, and 24 hours. Patients received standard intravenous tramadol doses at predetermined times up to a max of 300mg. Tramadol doses received by patients in the postoperative phase were converted to morphine equivalents. The study did not find any significant difference in time of first perception

of pain ($p=0.07$). Also, there was no statistically significant difference between groups in pain intensity levels either at rest or with activity the $p=0.38$ and 0.25 respectively (Bajracharya et al., 2019).

Dogan et al. (2016) evaluated intraoperative infusion of esmolol versus lidocaine's effect on postoperative pain intensity. Postoperative rest and dynamic (with activity) pain intensity was assessed using a VAS. Pain was assessed during the postoperative phase at 2-, 6-, 12-, and 24-hours intervals. Additionally, pain was assessed at 10- and 20-minutes post-extubation. VAS pain scores were only statistically significant at the 10- and 20-minutes post-extubation interval. Dynamic VAS pain scores at 10- and 20-minutes post-extubation were significantly higher in group L (lidocaine) compared to group E (esmolol), p value was 0.021 and 0.003 respectively. At rest VAS pain scores at 10- and 20-minutes post-extubation were significantly higher in group L (lidocaine) versus group E (esmolol), $p=0.017$ and 0.006 respectively. Of note, specific VAS pain scores were not reported by the authors. Only results with p that were significant were reported by the authors. These results suggest that intraoperative esmolol was more effective than lidocaine in decreasing postoperative pain intensity during immediate postoperative period (Dogan et al., 2016).

Duarte de Morais et al. (2020) compared intraoperative esmolol to placebo effect on postoperative pain intensity in patients undergoing gastropasty. Duarte de Morais et al. (2020) measured postoperative pain intensity using a numerical rating scale (NRS) at specific time intervals of arrival (T_0), 30 minutes followed by 1, 2, 6, 12, and 24 hours postop. The highest pain scores for esmolol group were reported at the 30-minute and 1-hour mark. In the placebo group pain scores were higher at the 30-minute and 1-hour mark with max pain scores of 6 and 8 out of 10 respectively. At the 30-minute and 1-hour interval the esmolol group pain scores were

5 out of 10 for both intervals and less than the placebo group ($p=0.032$ and 0.004 respectively). The esmolol group pain scores were lower at the 2-hour interval, 3 out of 10 compared to the saline group of 5 out of 10 ($p=0.002$). At the 6-hour interval the esmolol group had lower pain scores, 3 out of 10, versus the placebo group, 4 out of 10 ($p=0.047$). At the 24-hour interval patients in the esmolol group were also shown to have lower pain scores, 0, compared to the saline group pain score, 1 ($p=0.029$). At the T0, 12-hour intervals pain scores were similar and were not statistically significant. Pain scores were cumulatively lower over the entire 24-hour period in the esmolol group (Duarte de Morais et al., 2020).

A systematic review by Gelineau et al. (2018) pooled postoperative VAS pain scores from 688 patients from 11 studies were pooled together and reported as SMD using a plot digitizer computer program. Random-effects analysis and Breslow day test was utilized to assess for heterogeneity of outcomes. An I^2 of $>25\%$ was considered to have substantial inconsistency. In the first postoperative hour, patients who received an intraoperative infusion of esmolol had lower postoperative VAS pain scores compared to both control groups (opioid and crystalloid), $-0.60 = \text{SMD}$. However, these results were not statistically significant, $p=0.163$ (CI=95%). Heterogeneity in VAS pain scores were noted to be high, $I^2=95.9\%$. As previously stated, after meta-regression analysis was performed and heterogeneity was attributed to the crystalloid and opioid control groups. When intraoperative esmolol infusion was compared to crystalloid control group, postop VAS pain scores in the first hour were lower in the esmolol group, $-1.25 = \text{SMD}$ ($p \leq 0.001$, CI=95%, $I^2=89.9\%$). Inversely, in the first hour VAS pain scores in patients who received intraoperative esmolol had higher postop as compared to opioid control, $1.23 = \text{SMD}$. However, these results were not statistically significant ($p=0.207$, CI=95%, $I^2=97.2\%$; Gelineau et al., 2018).

Haghighi et al. (2015) assessed intraoperative esmolol infusion's effect on postoperative pain in patients who underwent surgical fix of single leg displaced fracture of tibia versus placebo. Postoperative VAS pain scores were lower in the esmolol group, 4.09 (+/-2.05), versus the placebo group, 6.29 (+/- 2.14) through the recovery period (PACU) (p value= 0.02). Additionally, VAS pain scores at 3- and 6-hours after surgery were lower in the esmolol group, 5.12 (+/-1.86) and 5.21 (+/-1.87) respectively; versus the placebo, 6.8 (+/-2.01) and 6.43 (+/- 1.48) respectively. The p for VAS pain scores at 3- and 6-hours after surgery were 0.001 and 0.0001 respectively, making these results statistically significant (Haghighi et al., 2015).

Ji et al. (2022) evaluated postoperative pain scores in patients undergoing laparoscopic cholecystectomy. As previously stated, participants were allocated into three groups esmolol, ramosetron and esmolol, and ramosetron. Postoperative VAS pain scores were reported as a mean +/- SD. Ji et al. (2022) found that patients who received intraoperative esmolol as a single agent had reduced VAS pain scores at the 30-minutes postoperative interval. VAS scores in group E (esmolol) and E+R (esmolol and ramosetron) had average scores of 3.62 (+/- 1.00) and 3.62 (+/-1.00) respectively. Group E and E+R's postoperative VAS pain scores were noted to be less compared to the group R (ramosetron) 5.72 (+/-1.41) ($p<0.001$; Ji et al., 2022).

Lee & Lee (2010) evaluated postoperative pain in patients who received propofol and remifentanil based TIVA's for laparoscopic appendectomy using a VAS (0-100). Postoperative pain was evaluated at 30-minute as well as the subsequent 6- and 24-hours postoperative intervals. VAS pain scores were reported as a mean. At the 30-minute interval's mean pain score in group E (received intraoperative esmolol infusion) was 45.1 (+/- 2.4) and group C (received no intraoperative esmolol infusion) was 60.2 (+/-4.2). These results were statistically significant as the p was 0.014. At the 6- and 24-hour postoperative interval, pain scores were lower in the

esmolol group 23.2 (+/-6.1) and 17.3 (+/- 4.5), compared to control group 33.5 (+/- 6.3) and 23.4 (+/- 5.3) respectively. However, the *p* value for the 6- and 24-hour intervals did not meet statistical significance (Lee & Lee, 2010).

Lopez-Alvarez et al. (2012) assessed postoperative pain intensity using a visual numerical rating scale (VNRS, 0-100). Postoperative pain was assessed at 30, 60, 120, 180 minutes in the PACU. Group E received intraoperative esmolol infusion and group R-K received intraoperative ketamine and remifentanyl infusions. VNRS pain scores were reported as a median score +/- SD. At all the postoperative time intervals the PACU pain scores were lower in group E than group R-K. The highest pain score in group E was 2 while in group R+K it was 4 (*p*= 0.01). Group E's pain scores were lower on average by 11 points compared to group R-K (*p*<0.05, CI=95%; Lopez-Alvarez et al., 2012).

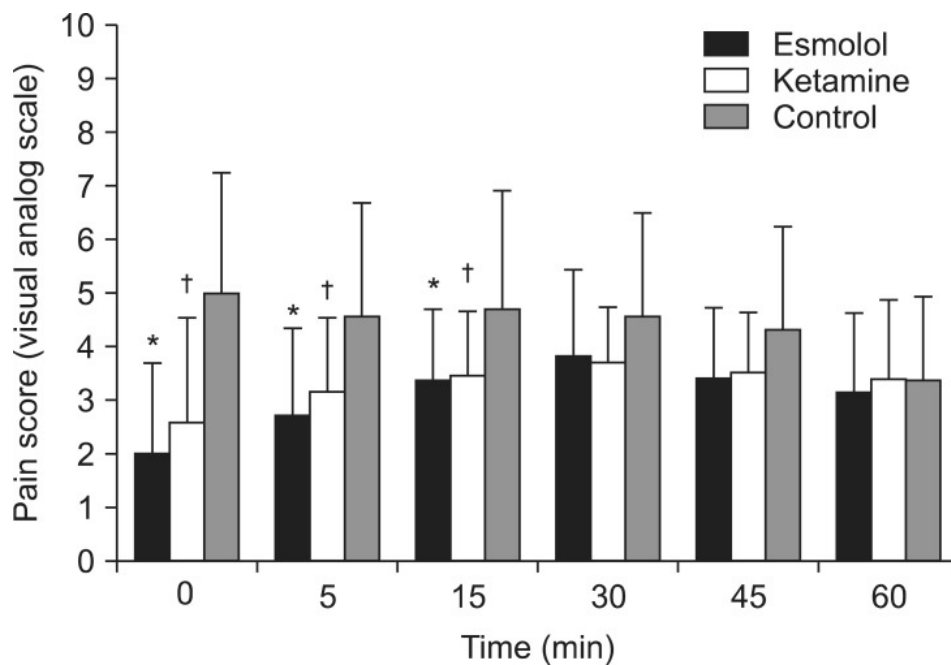
Mahrose & Elgharabawy (2020) measure postoperative pain intensity in patients who received intraoperative esmolol infusion versus placebo. Pain was scored using a VAS. In the PACU, pain was assessed every 30 minutes. Pain was subsequently assessed every hour for the first 4 hours followed by every 4 hours for the next 24 hours. In the first 4-hour postoperative interval the range of VAS pain scores for the esmolol group was lower than the placebo group, 1.00 to 6.64 and 5.10 to 6.31 respectively (*p*<0.0001; Mahrose & Elgharabawy, 2020).

As previously stated, Lee et al. (2014) conducted a prospective RCT that compared the efficacy of intraoperative esmolol and ketamine infusions on postoperative pain in patients between the ages of 20-70 years of age that underwent laparoscopic cholecystectomy. Sixty patients were allotted into three groups a ketamine, esmolol, and control group. The control group received an intraoperative infusion of remifentanyl only with a placebo of equivalent volume to the study drugs. The esmolol group received an intraoperative esmolol infusion and

the ketamine group received an intraoperative infusion of ketamine in addition to a remifentanyl infusion. Pain was measured using a VAS (0-10) and reported as a mean +/-SD. Pain was assessed on arrival to the recovery unit, followed by every 15 minutes for the first postoperative hour. The esmolol and ketamine groups had significantly lower pain scores compared to the control group (remifentanyl only) through the entire postoperative period ($p < 0.05$). Postoperative pain scores were not statistically different between the ketamine and esmolol groups ($p > 0.05$; see Figure 2; Lee et al., 2014).

Figure 2

Postoperative VAS Pain Scores



Note. Figure adapted from “Comparison of effects of intraoperative esmolol and ketamine infusion on acute postoperative pain after remifentanyl-based anesthesia in patients undergoing laparoscopic cholecystectomy,” by Lee, M.H., Chung, M.H., Han, C.S., Lee, J.H., Choi, Y.R., Choi, E.M., Lim, H.K., Cha, Y.D. (2014). *Korean Journal of Anesthesiol*, 66(3), 222-229. <https://dx.doi.org/104097/kjae.2014.66.3.222>

Watts et al. (2017) conducted a systematic literature review and meta-analysis of pain scores in the first 6 hours of the postoperative interval in patients who received intraoperative esmolol infusions versus placebo. Pain scores from studies reviewed were determined using

VAS and NRS (0-10). The postoperative pain scores were pooled and reported as a single-value mean score. Patients who received intraoperative esmolol infusions had reduced pain scores in the first 6 hours of the postoperative interval by a mean of 1.16 compared to the placebo group ($p < 0.005$, CI=95%; Watts et al., 2017).

Ketamine and Postoperative Opioid Consumption

Mercanoglu et al. (2022) conducted a prospective RCT that studied postoperative morphine consumption in patients who underwent elective laparoscopic cholecystectomy who received either intraoperative ketamine, dexmedetomidine, and remifentanyl. Patients in all three groups received remifentanyl infusions during the intraoperative phase. Patients were randomized into three groups, ketamine, dexmedetomidine, and control (remifentanyl only). The control group, which received intraoperative remifentanyl only. The other groups received either intraoperative infusions of ketamine or dexmedetomidine in addition to a remifentanyl infusion. Morphine consumption was measured in the postoperative phase and was reported as a mean +/- SD. Follow up was at the 48-hour postoperative interval. In the postoperative phase in addition to a morphine PCA, patients received rescue analgesia for VAS pain scores >4 (Mercanoglu et al., 2022).

In the postoperative phase Mercanoglu et al. (2022) determined the dexmedetomidine and ketamine groups had similarly lower morphine requirements compared to the control group. This trend in postoperative opioid consumption among the groups reached statistical significance at all postoperative time points. The total amount of morphine administered in the postoperative phase for the ketamine group was 6.33 mg (+/-1.71 mg), the dexmedetomidine group was 10 mg (+/-1.50 mg), and the control group was 17.60 mg (+/-6.41 mg). The ketamine group had significantly lower morphine requirements compared to both the dexmedetomidine and control

groups ($p < 0.001$). Dexmedetomidine group had lower morphine requirements compared to the control group ($p < 0.001$). Additionally, at the 4-hour postoperative interval patients in the ketamine group had significantly lower morphine requirements, 3.33 mg (± 1.26 mg) compared to the dexmedetomidine group 7.40 mg (± 1.67 mg), and the control group 12.27 mg (± 3.54 mg) ($p < 0.001$). In the postoperative phase only 30% of patients in the ketamine group (9 patients out of 30) required rescue analgesia. By contrast the percentage of patients who required rescue analgesia in the dexmedetomidine group was 50% (15 out of 30) and the control group was 93.3% (28 out of 30). When compared to each other the percentage of patients who required rescue analgesia in the postoperative phase were lower in the ketamine group ($p < 0.001$; Mercanoglu et al., 2022).

Moro et al. (2017) studied the efficacy of different intraoperative ketamine doses to placebo on postoperative opioid consumption measured in mean morphine consumption \pm SD. Patients were allotted to three groups K2, K4, and S. The lower dose ketamine group K2 received 0.2 mg/kg of ketamine. The higher dose ketamine group K4, received 0.4mg/kg of ketamine. Group S received a placebo of equivalent volume. The mean morphine consumption between the K2 and K4 groups were 1.2 mg (± 2.2 mg) and 1.2 mg (± 1.7 mg) respectively. Thus, there was no statistically significant difference in postoperative opioid consumption between the two ketamine groups. The placebo group S had a mean postoperative morphine consumption of 1.6 mg (± 2.2 mg). Interestingly, there was no statistically significant difference in morphine consumption between the placebo group and either ketamine groups. The p for all three groups was 0.509 (No CI reported). Additionally, tramadol consumption (reported as mean \pm SD) was 2mg, 4mg, and 6mg in the placebo, K2, and K4 respectively ($p = 0.37$, no CI reported; Moro et al., 2017).

In a systematic review and metanalysis of RCT's, Wang et al. (2021) investigated the intraoperative use of esketamine versus placebo's effect on postoperative morphine consumption. Morphine consumption was evaluated at the 4-, 12-, and 24-hour postoperative time intervals. Morphine consumption was reported as SMD. At the 4-hour postoperative interval, the morphine consumption was significantly less in the esketamine groups as compared to the placebo group with a SMD of -0.98 ($p < 0.00001$, CI=95%, $I^2=0\%$). At the 12-hour postoperative interval, morphine consumption was lower in the esketamine group compared to placebo with a SMD of -1.36 ($p=0.003$, CI=95%, $I^2=79\%$). There was no statistically significant difference in morphine consumption between the groups at the 24- and 48-hour postoperative intervals, SMD was -0.70 ($p=0.06$, CI=95%, $I^2=88\%$) and -0.79 ($p=0.39$, CI=95%, $I^2=94\%$) respectively (Wang et al., 2021).

Ye et al. (2017) assessed postoperative narcotic requirements in patients who received intraoperative ketamine infusions versus placebo. Narcotic requirements were measured in morphine equivalents. These results were reported as SMD at the 12-, 24-, and 48-hour postoperative intervals. Results revealed that at all postoperative time intervals postoperative narcotic requirements were significantly less in patients who received intraoperative ketamine infusions. At the 12-hour postoperative interval patients who received intraoperative ketamine consumed less narcotics compared to placebo, SMD -0.296 ($p=0.033$, CI=95%, $I^2=0\%$). At the 24-hour postoperative interval patients consumed less narcotic in the ketamine group, SMD -0.310 (p value= 0.025, CI=95%, $I^2=0\%$). At the 48-hour postoperative interval patients in the ketamine group consumed less narcotic, SMD -0.338 ($p=0.015$, CI=95%, $I^2=0\%$; Ye et al., 2017).

Zhu et al. (2018) systematic literature review of postoperative opioid consumption in patients who underwent laparoscopic cholecystectomy and received intraoperative ketamine versus placebo. Postoperative opioid consumption was measured at 12-, 24-, and 48-hour postoperative intervals. Postoperative opioid consumption was reported as a weighted mean difference (WMD). In six studies a forest plot was used to evaluate postoperative opioid consumption at the given postoperative time intervals. Zhu et al. (2018) found that at all postoperative intervals opioid consumption was decreased in patients who received intraoperative ketamine, -2.820, -3.816, and -2.210 respectively. However, only at the 12- and 24-hour postop interval were these results statistically significant $p=0.019$ and 0.025 respectively (CI=95% at all intervals; Zhu et al., 2018).

Ketamine and Postoperative Pain Intensity

A prospective RCT study conducted by Mercanoglu et al. (2022) measured postoperative pain intensity in patients who underwent elective laparoscopic cholecystectomy. Patients were randomized into three groups ketamine, dexmedetomidine, and control (remifentanyl only). All groups received an intraoperative infusion of remifentanyl. Postoperative pain was measured using a VAS (0-10 scale) at arrival to recovery unit followed by 4-, 8-, 24, and 48-hour intervals. Pain scores were pooled and reported as a mean \pm SD. The ketamine group's pain scores at arrival to recovery unit and 4-, 8-, 12-, 24-, and 48-hour postoperative intervals were 3.17 (\pm 0.46), 3.37 (\pm 0.77), 3.77 (\pm 0.97), 3.90 (\pm 0.66), and 3.0 (\pm 0.53) respectively. The dexmedetomidine group's pain scores at arrival to the recovery unit and 4-, 8-, 12-, 24-, 48-hour postoperative interval were 4.60 (\pm 0.68), 4.47 (\pm 0.51), 4.43 (\pm 0.77), 3.47 (\pm 0.51), and 3.07 (\pm 0.25) respectively. The control group's pain scores at arrival to the recovery unit and 4-, 8-, 12-, 24-, 48-hour postoperative interval were 6.33 (\pm 1.47), 4.97 (\pm 0.85), 4.80 (\pm 0.76),

3.90 (+/- 0.80), and 2.93 (+/- 0.37) respectively. At all the postoperative time intervals the postoperative VAS pain scores were lower in the ketamine and dexmedetomidine group compared to the control group ($p < 0.05$; Mercanoglu et al., 2022).

Moro et al. (2017) assessed the effect of different ketamine doses administered during the intraoperative phase on postoperative pain intensity. Pain intensity was evaluated using a NRS scale where 0 was no pain to 10 being the highest level of pain perceived by the patient. NRS pain scores were pooled and reported as a mean and SMD (Moro et al., 2017). Moro et al. (2017) found that there was no statistically significant difference in postoperative pain intensity between the lower and higher dose ketamine groups. The postoperative NRS pain scores for group K4 (0.4 mg/kg ketamine) and K2 (0.2 mg/kg ketamine) were 2.8 (+/- 3.0) and 2.6 (+/- 3.2) respectively. Additionally, there was no statistically significant difference in postoperative NRS pain scores in group S (placebo) 3.8 (+/- 2.8) compared to the previously mentioned postoperative NRS pain scores of the K2 and K4 groups (p for placebo, K2, and K4 = 0.27, no CI reported; Moro et al., 2017).

Wang et al. (2021) performed a systematic review of intraoperative ketamine infusion versus placebo of equivalent volume. Postoperative pain was assessed with activity (dynamic) and at rest. Studies in this review measured postoperative pain using either VAS or NRS scales. Pain was assessed at 4-, 12-, and 24-hour postoperative intervals. Postoperative pain scores were pooled together and using a forest plot to determine and report the SMD. At the 4-, 12-, 24-hour postoperative intervals the at rest pain scores were lower in the ketamine group than in the control group, -1.11 SMD ($p < 0.00001$, CI=95%, $I^2=73%$) and -0.88 SMD ($p=0.001$, CI=95%, $I^2=83%$), -0.39 ($p=0.02$, CI=95%, $I^2=80%$) respectively. There were no statistically significant differences in dynamic pain scores in either group at any time intervals (Wang et al., 2021).

Ye et al. (2017) evaluated postoperative pain intensity at 12-, 24-, and 48-hour postoperative intervals in patients who received intraoperative ketamine infusions versus placebo. Postoperative pain was measured using a VAS. VAS pain scores were analyzed using fixed-effects model. No significant heterogeneity was noted at any of the postoperative time intervals as was $I^2 < 10\%$. Pooled postoperative VAS pain scores were reported as SMD. At the 12-, 24-, and 48-hour postoperative time intervals, VAS pain scores were less in the ketamine group compared to the placebo group -0.322, -0.332, and -0.340 respectively. These results all reached statistical significance as p for 12-, 24-, and 48-hour intervals were 0.020, 0.017, and 0.014 respectively (CI=95% for all time intervals; Ye et al., 2017).

Zhang et al. (2022) assessed postoperative pain using aNRS scale at 15 and 30-minutes post-extubation in patients who received intraoperative esketamine versus placebo. NRS pain scores were further categorized by the number of patients reporting NRS pain scores in specific ranges, NRS 0, NRS 1-3, and NRS >4. Zhang et al. (2022) found that pain scores were less in the esketamine group at the 15-minute post-extubation interval but had no difference in pain scores between groups at the 30-minute post-extubation interval. At the 15-minute post-extubation interval there were significantly more patients in the esketamine group, 14 out of 23 that reported 0 pain compared to 8 out of 24 in the placebo group. Only 9 of 23 patients in the esketamine group reported a NRS pain score of 1-3 at the 15-minute post-extubation interval. Lastly, 0 participants reported NRS score of >4 at the 15-minute post-extubation interval. At the 15-minute post-extubation interval the placebo group had 14 out of 24 patients report a NRS pain score of 1-3 and 2 patients out of 24 reported a NRS pain score >4. These results had a cumulative p value of 0.012 making these results statistically significant (No CI reported). At the 30-minute post-extubation interval the esketamine group had 18 out of 23 patients report a NRS

pain score of 0, 5 out of 23 patients had a NRS pain score of 1-3, and 0 patients had a NRS pain score of >4. At the 30-minute post-extubation interval the placebo group had 12 out of 24 patients report a NRS pain score of 0, 12 out of 24 patients reported a NRS pain score of 1-3, and 0 patients reported a NRS pain score of >4. However, these results failed to reach statistical significance as the cumulative $p=0.117$ (no CI reported; Zhang et al., 2022).

Zhu et al. (2018) conducted a meta-analysis of RCT's that studied the effect of intraoperative ketamine infusions versus placebo on postoperative pain intensity in patients who underwent laparoscopic cholecystectomy. Zhu et al. (2018) found 6 studies that assessed postoperative VAS pain scores at 12-, 24-, and 48-hours. Postoperative pain scores from these studies were reported as WMD. Compared to the placebo group, patients who received an intraoperative ketamine infusion had significantly lower VAS pain scores -0.478, -0.550, and -0.350 at the 12-, 24-, and 48-hour postoperative intervals respectively. These results reached statistical significance at the 12-, 24-, and 48-hour postoperative time intervals where $p=0.040$, 0.049 , and 0.037 respectively (CI= 95% at all intervals; Zhu et al., 2018).

Limitations & Literature Gaps

This literature review was presented with several limitations. First there were only three small studies that directly compared intraoperative esmolol and ketamine Lee & Lee (2010), Lee et al. (2014), and Lopez-Alvarez et al. (2012). Although Lopez-Alvarez et al. (2012) did compare the intraoperative use of esmolol and ketamine it lacked a control group and only the ketamine group received remifentanyl. Therefore, in Lopez-Alvarez et al. (2012) the increased postoperative opioid requirements of the ketamine-remifentanyl group could be attributed to remifentanyl's well-established tendency to cause secondary opioid induced hyperalgesia (Nagelhout & Elisha, 2018).

Heterogeneity was high in the systematic literature reviews included in this literature review secondary to different surgeries, different drug dosing, follow up times, pain scoring systems, and quantifiable results. For example, Gelineau et al. (2018) included laparoscopic gynecologic surgeries, appendectomy, cholecystectomy, as well as, orthopedic, lower abdominal procedures, septorhinoplasty, and lower abdominal (including open total abdominal hysterectomy) procedures into their literature review. The different esmolol infusion rates as well as the inclusion or exclusion of loading doses in the esmolol groups contributed to high heterogeneity in the systematic literature reviews included in this literature review.

In this literature review no study assessed dose response curves except for Chen et al. (2020), which assessed dose response curves of ketamine. Thus, this review was unable to establish an effective dose of esmolol during the intraoperative period.

In the 31 studies reviewed there were few studies that were multicentered or had a large sample size. Lopez-Alvarez et al. (2012) was the only multicentered study that could be included in this literature review. Most of the studies had less than 150 participants, which could contribute to a higher risk of bias. Studies in this literature did attempt to limit bias by double-blind method and random assignment of participants to groups. Bhattacharjee et al. (2016) was the only single-blinded study included in this literature review. Studies were limited to patients with an ASA status of I and II, but future research should specifically study patients with ASA physical status of III and IV.

Discussion

When measured in terms of opioid consumption and pain intensity scores in ASA I and II patients undergoing laparoscopic cholecystectomy, esmolol can improve postoperative

nociception regardless of the analgesia modality regional anesthesia, non-opioid adjunct, placebo, and traditional opioids.

In all studies where esmolol was compared to placebo, this literature review determined that patients who received intraoperative esmolol infusions experienced lower postoperative pain scores and opioid consumption. Interestingly, in Lopez-Alvarez et al. (2012) and Lee & Lee. (2010) which compared the use of intraoperative esmolol infusions to intraoperative remifentanyl and/or ketamine infusions, found that patients who received an intraoperative esmolol infusions had lower postoperative pain scores and opioid consumption. Lee et al. (2014) found no statistically significant difference between intraoperative esmolol or ketamine on postoperative pain intensity or opioid consumption. Additionally, Lee et al. (2014) determined that intraoperative ketamine or esmolol were more effective than remifentanyl in reducing postoperative pain intensity and opioid consumption. Ji et al. (2022) found no difference in postoperative pain scores in patients who received an intraoperative infusion of esmolol versus intraoperative ketorolac doses. Ji et al. (2022) found lower postoperative ketorolac requirements in the esmolol group, suggesting that esmolol can be an effective non-opioid adjunct as ketorolac. In Dogan et al. (2016), patients who received intraoperative lidocaine infusions, experienced higher pain scores than in patients who received intraoperative esmolol infusions. Despite higher postoperative pain scores in the lidocaine group, Dogan et al. (2016) found there was no difference in postoperative opioid consumption between either group. Bajracharya et al. (2019) also compared intraoperative esmolol versus lidocaine infusions and found there was no statistically significant difference in postoperative pain scores or opioid consumption between the groups. Both studies suggest that an intraoperative infusion of esmolol may be as effective as lidocaine in decreasing postoperative pain intensity and opioid consumption. When

intraoperative esmolol infusions were compared to intraoperative opioid use, Gelineau et al. (2018) determined there was no statistical difference in postoperative pain intensity.

Additionally, Gelineau et al. (2018) found patients in the esmolol group had lower opioid requirements. Abdelfatah & Amin (2021) determined that patients who received intraoperative esmolol had lower postoperative pain scores and opioid consumption when compared to patients who received a TAP block.

Overall, these results suggest that while intraoperative esmolol may not consistently lower postoperative pain intensity it does decrease postoperative opioid consumption. The decrease in postoperative opioid consumption consistently noted across multiple studies in this literature review requires further research to elucidate if esmolol influences the perception of pain, what its mechanism of action in nociception is, and how it decreases subsequent need for analgesia in the postoperative phase.

This literature review determined that patients who received intraoperative ketamine experienced lower postoperative pain intensity and opioid consumption when compared to opioids, other non-opioid adjuncts, and placebo. As previously stated, Lopez-Alvarez et al. (2012) determined that patients who received an esmolol infusion as a sole intraoperative agent had lower opioid and pain intensity as compared to patients who received intraoperative remifentanil and ketamine infusions. However, Lopez-Alvarez et al. (2012) did not address the known side effect of hyperalgesia in patients who receive remifentanil infusions. Although secondary hyperalgesia produced by remifentanil is a concern, Lee et al. (2014) utilized remifentanil as a control when comparing intraoperative esmolol and ketamine. Lee et al. (2014) subsequently found no difference in postoperative pain intensity or opioid consumption between

either esmolol or ketamine. Thus, showing that esmolol maybe an effective non-opioid adjunct as ketamine, however further research is required to definitively make this conclusion.

Conclusion

The definitive treatment for acute cholecystitis is removal of the gall bladder commonly performed utilizing the laparoscopic technique (Hines & Marschall, 2018). The obesity and opioid epidemics continue to be at the forefront of health care in the United States. Patients with these conditions will inevitably experience changes in their health status that may require routine surgical procedures such as laparoscopic cholecystectomy. Despite the decrease in opioid prescriptions and the rise in opioid sparing and free anesthetic techniques the misuse of opioids continues to negatively impact patients. Subsequently, the demand for opioid free multimodal anesthesia that may include medications like esmolol and ketamine, will continue to be at the forefront of anesthesia research and practice.

CRNAs provide 65% of all the anesthetic administered in the United States (NMANA, 2023). In the United States, CRNA's are often the only anesthesia providers in rural, underserved, and vulnerable areas (AANA, 2023). CRNAs are uniquely positioned to not only improve their patients postoperative experience, but to provide and advocate for interventions that will significantly impact the current opioid epidemic.

This literature review has determined that ketamine and esmolol can equally reduce postoperative pain intensity and opioid consumption in patients undergoing laparoscopic cholecystectomy when compared to placebo, other nonopioid adjuncts, and opioids. Thus, demonstrating that they are part of a larger more dynamic and patient centered approach to the treatment and prevention of postoperative pain.

Future Research

Esmolol's role as a non-opioid adjunct requires more research as its mechanism of action in nociception is poorly understood. Determining its effectiveness in decreasing postoperative pain intensity and opioid consumption have been limited by small sample size studies, lack of controls, and high heterogeneity. Whether ketamine is more effective than esmolol in reducing postoperative pain and opioid consumption requires further research.

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