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Is Perioperative Intravenous Lidocaine a Sufficient Adjunct to Traditional Opioid Therapy at Decreasing Post-operative Pain in Male and Female Patients Ages 18-75 Following a Laparoscopic Cholecystectomy?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine "Is perioperative intravenous lidocaine a sufficient adjunct to traditional opioid therapy at decreasing post operative pain in male and female patients ages 18-75 following a laparoscopic cholecystectomy?"

STUDY DESIGN: A review of three randomized control trials (RCTs) that were peer reviewed and published in English after 2015.

DATA SOURCE: All articles were published in peer reviewed journals and were researched using PubMed and EBSCO databases. Studies were selected based on their ability to answer the question posed in the objective, and if the researched outcomes were patient oriented.

OUTCOMES: The outcome assessed was the reduction in post-operative pain scores during the studies. Pain scores were recorded using visual analogue scales or visual numerical scales.

RESULTS: One out of the three studies have found that lidocaine is a sufficient adjunct to traditional opioid therapy at reducing post-operative pain scores in patients following laparoscopic cholecystectomies. Song et al. (2017) showed significant data at 2 hours post-operation for the mean pain scores of the lidocaine group and placebo group (lidocaine 3.01 $\pm$0.65 vs. placebo 4.27 $\pm$0.58, $p = 0.01$). However, studies by Ortiz et al. (2016) and Bajracharya et al. (2019) found non-significant data. Ortiz et al. found that at 2 hours post-operation mean scores between the two groups were (lidocaine 2.57 $\pm$ 2.31 vs. placebo 2.14 $\pm$ 1.73, $p = 0.50$). The study by Bajracharya et al. concluded that the mean score for the lidocaine group was 1.8 and the esmolol group was 1.6. No p-value was calculated at 2-hours post-operation for this study but the overall p-value at the end of the study was non-significant ($p = 0.38$).

CONCLUSIONS: The results of these three studies revealed that it remains unknown if lidocaine is a beneficial adjunct to traditional opioid therapy at decreasing post-operative pain in patients following laparoscopic cholecystectomies. More research is needed to determine the optimal dosing and infusion rate to administer during the procedures.

KEYWORDS: Lidocaine, laparoscopic cholecystectomy

INTRODUCTON:

Approximately 20 million people in the United States are affected by gallbladder disease annually.[1] Gallbladder disease occurs many ways and most commonly is associated with poor function and super concentrated bile. These conditions lead to the formation of gallstones which are a major cause of gallbladder disease. There are three types of gallstones: cholesterol, brown, and black. Cholesterol stones are the most common and precipitate due to high concentrations of cholesterol within the gallbladder.[1] Black stones form from hemolytic diseases and brown stones from infection. Obstruction in one of the ducts (cystic or common bile) leads to inflammation and infection of the organ.[1] Occasionally, an acute process can occur in the absence of a stone known as acalculous cholecystitis.[1]

A classic symptom of gallbladder disease is right upper quadrant or epigastric pain. Acutely, this pain is exacerbated by the consumption of high fat meals.[1] Onset usually occurs between 30 minutes and 2 hours after consuming fatty foods and can last up to 24 hours.[1] It is usually a sharp pain with radiation to the right flank and occasionally right shoulder blade. This is due to sympathetic innervation.[1] Once the disease becomes chronic exacerbations can occur regardless of oral intake.[1]

The incidence of gallbladder disease among Americans is continuously increasing. In the United States alone gallbladder disease accounts for approximately 2.2 million hospital visits each year.[2] Treatment for these patients begins conservative however, the only definitive treatment is a cholecystectomy. Indications for open and laparoscopic cholecystectomies include cholecystitis (acute/chronic), symptomatic cholelithiasis, biliary dyskinesia, acalculous cholecystitis, gallstone pancreatitis, and gallbladder masses/polyps.[3] While both procedures are sufficient, a laparoscopic cholecystectomy is now considered the gold standard. This places a

significant economic burden on the healthcare system of the United States. As it is the most common abdominal procedure performed, over 900,000 procedures annually, laparoscopic cholecystectomies total $5 billion in healthcare expenditures each year.[4]

Despite the economic burden, performing a cholecystectomy laparoscopically vs open offers many benefits. It is a minimally invasive procedure that results in less post-operative pain, better cosmesis, and shorter hospital stays.[3] Although there is less pain than the open method, like any surgery patients still experience some level of pain and require management. Traditional pain management following surgery is opioid therapy such as fentanyl and morphine.[5,6] However, the use of opioids has shown many adverse effects. Common adverse effects include exacerbation of post operative ileus, longer hospital stays, constipation, and high rates of misuse and addiction.[5] Due to these undesirable effects, new analgesic methods in this patient population are of extreme importance.[6]

Perioperative intravenous lidocaine as pain management for patients receiving laparoscopic cholecystectomies is being researched as a possible adjunct to opioids. Lidocaine possesses analgesic and anti-inflammatory properties however the optimal dose remains uncertain. Different doses of lidocaine have different effects on pain.[5] Studies have shown that small doses suppress ectopic impulse generation, moderate doses suppress central sensitization, and in large doses it has a general analgesic effect.[5] Further research is needed to determine what dose of lidocaine would be most beneficial.

Lidocaine has shown success at reducing post operative pain following major abdominal procedures.[6] This is due to its ability to suppress the inflammatory response that occurs during surgery. Specifically, research has shown that lidocaine suppresses the inflammatory markers IL-8, IL-6, and IL-1ra.[5] Since it is the same inflammatory process that occurs during minimally

invasive procedures, just to a lesser extent, researchers are hopeful that lidocaine can provide the same benefit in a laparoscopic setting. This paper aims to evaluate three randomized control trials and the efficacy of perioperative intravenous lidocaine in conjunction with traditional opioid therapy at reducing post-operative pain following laparoscopic cholecystectomies.

OBJECTIVE:

The objective of this systematic EBM review is to determine "Is perioperative intravenous lidocaine a sufficient adjunct to traditional opioid therapy at decreasing post operative pain in male and female patients ages 18-75 following a laparoscopic cholecystectomy?"

METHODS:

Scholarly literature and resources were selected for this paper based on their ability to answer the question: Is perioperative intravenous lidocaine a sufficient adjunct to traditional opioid therapy at decreasing post operative pain in male and female patients ages 18-75 following a laparoscopic cholecystectomy? The articles were also selected because they include patient-oriented outcomes (POEMs), in this case the decrease in post-operative pain. All articles were published in peer reviewed journals in English. PubMed and EBSCO: Academic Search Premier, Alt HealthWatch, AMED – The Allied and Complementary Medicine Database, and CINAHL Plus databases were used to find these resources. Inclusion criteria included free full text, randomized control trials, and those that were published after the year 2015. Articles were excluded if they were meta-analysis, focused on other outcomes besides pain, and were published before the year 2015. All studies included are double blind, randomized control trials published in the years 2016, 2017, and 2019 and found using the key words cholecystectomy, pain, and lidocaine. Statistics were reported and used as standard deviations, median scores, and p-values. Table 1 includes characteristics and demographics of the included studies.

Table 1. Demographics and Characteristics of Included Studies

Study	Type	# Patients	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Bajrachary a (2019)[7]	Randomized Control Trial	90	Females 18-60 years of age	Any female age 18-60 with a physical status of 1 or 2 according to the American society of Anesthesiologists who are undergoing a laparoscopic cholecystectomy under general anesthesia.	Anyone with a mental impairment that would cause them to not understand the VAS, current use of opioids or beta-adrenergic receptor antagonists, and anyone with chronic pain other than cholelithiasis	4	Intravenous (IV) lidocaine bolus vs. IV bolus of esmolol
Ortiz (2016)[6]	Randomized Control Trial	44	Adults 18-75 years of age	Anyone age 18-75, male and female, with a physical status according to the American Society of Anesthesiologists of 1 and 2 and undergoing a laparoscopic cholecystectomy under general anesthesia	Those who are older than 75, h/o chronic opioid use, CV disease, and those who require an open procedure	1	Intravenous lidocaine vs. saline (placebo)
Song (2017)[5]	Randomized Control Trial	80	Adults 18-65 years of age	Anyone age 18-65, male and female, undergoing a laparoscopic cholecystectomy under general anesthesia	Individuals who require an open procedure, have chronic pain, and those who take analgesics daily	9	Intravenous lidocaine vs. equal volume of saline (placebo)

OUTCOMES:

Outcomes were measured by the decrease in post operative pain scores following laparoscopic cholecystectomies in all three studies. Patient reported pain scores were measured using the visual analogue scale (VAS) in Song and Bajracharya studies and the visual numeric scale (VNS) in the Ortiz study. A score of 0 indicated “no pain” and a score of 10 was indicative

of "worst imaginable pain" for the VAS and VNS.[5,6,7] Pain scores were recorded post-operatively at 1, 2, 4, 12, and 24 hours in the Ortiz study, 2, 6, 12, and 24 hours in the Bajracharya study, and at 2, 6, and 24 hours in the Song study.[5,6,7] To keep consistency between all studies, this review will only focus on VAS pain scores at 2 hours post-operation for each group and the other endpoints of all studies will not be discussed.

RESULTS:

Song et al. (2017) conducted a randomized, blinded placebo-controlled trial that was conducted at a tertiary university hospital in Beijing, China from December 2015 to December 2016.[5] A total of 80 patients, ages 18 – 65 years old, were recruited and met the requirements to be participants in the study.[5] Patients were selected based on the inclusion and exclusion criteria in Table 1. Participants were randomized into either the lidocaine infusion or saline placebo group using computer generated codes that were concealed in sequentially numbered opaque envelopes.[5] An independent anesthesiologist who was not involved in the study was assigned the role of opening the sealed envelopes which contained patient allocation and prepare the designated solution.[5] Syringes were labeled with a case number to keep the participating anesthesiologist, study participants, and perioperative staff blind of the treatment.[5] Individuals assigned to the lidocaine infusion group received an IV bolus of lidocaine (1.5 mg/kg slowly over 10 minutes) 30 minutes before any skin incision was made followed by a continuous IV infusion of lidocaine at a rate of 2 mg/kg/h.[5] Patients in the saline placebo group were given an equal volume of 0.9% normal saline in the same manner. All patients were given the same perioperative and post operative management. The groups only differed in lidocaine infusion or normal saline. When the procedure was complete, three patients from the control group and four patients from the lidocaine group were excluded due to conversion to open surgery. There were

also two dropouts from the control group due to unqualified blood samples, making a total of nine withdrawals.[5] A total of 71 patients (35 in the placebo group and 36 in the lidocaine group) completed the study.[5]

In the post-operative anesthesia unit (PACU) all participants were connected to a patient-controlled intravenous analgesia (PCIA) pump. The PCIA pump contained fentanyl and was set at a bolus of 20 μg with a 10-minute lockout interval.[5] There was no basal infusion. Table 2 depicts the mean pain scores of the lidocaine and placebo-control groups and standard deviation (± STD) at 2 hours after the completion of the operation. A p-value < 0.05 after treatment with lidocaine was considered statistically significant.[5] At 2 hours post-operation the mean pain scores in the lidocaine group were significantly lower than the placebo-control group (lidocaine 3.01 ±0.65 vs. placebo 4.27 ±0.58, $p = 0.01$).[5]

Table 2. VAS Pain Score Mean ± STD Difference Between Lidocaine Group and Placebo-control Group at 2 – hours Post Operation and Statistical Significance in the Song et al. Study[5]

Time	Placebo-control Group (n = 35)	Lidocaine Group (n = 36)	P – value
2-hr post-operation	4.27 ± 0.58	3.01 ± 0.65	0.01

Ortiz et al. (2016) conducted a double-blind, randomized, placebo-controlled trial that was developed in Santa Maria, Rio Grande do Sul, Brazil from July 2013 to February 2014.[6] A total of 87 patients were referred from outpatient clinics to be eligible for this study.[6] After analysis, 29 were eliminated based on the exclusion criteria listed in Table 1 and 14 patients refused to sign the consent form. The remaining 44 patients, all 18 years of age or older, were recruited into the study.[6] A computer program was used for randomization which generated random number sequences and placed them into two columns, 22 sequences per column.[6] A pharmacist employee from where the surgeries were performed was responsible for assigning

each column with a group (lidocaine and placebo), and the results were sealed in 44 envelopes.[6] The same employee was responsible for preparing the solutions and placing them in identical color and volume containers. Just before the induction of anesthesia, the anesthetist who was blind to the treatment, was provided with the corresponding patient syringe. Patients in the lidocaine group received a 1.5 mg/kg bolus of 0.3% lidocaine at the start of the procedure and were maintained at a dose of 3 mg/kg/h until one hour after surgery.[6] For the placebo group, saline was administered at the same infusion rates. All patients were given the same perioperative and post-operative treatment with the only difference being lidocaine vs. placebo. At the end of the procedure, one more patient from the lidocaine group was excluded due to conversion to an open procedure.[6] Data for this study was analyzed based on 21 patients from the lidocaine group and 22 patients from the placebo group.[6]

In post-operative recovery all patients were give a PCIA pump of morphine. The pumps were programmed with a 4 mL bolus (morphine solution 0.5 mg/mL) and had a lockout of 8 minutes between doses.[6] There was no continuous infusion of morphine used. Table 3 depicts the mean visual analogue scale (VNS) scores at 2-hours post-operation and STD for the lidocaine and placebo-control groups. A p-value < 0.05 after treatment with lidocaine was considered statistically significant.[6] At 2-hours post-operation there was no significant difference between the mean pain scores of the lidocaine group vs the placebo group (lidocaine 2.57 ± 2.31 vs. placebo 2.14 ± 1.73, $p = 0.50$).[6]

Table 3. VNS Pain Score Mean ± STD Difference Between Lidocaine Group and Placebo-control Group at 2 – hours Post Operation and Statistical Significance in the Ortiz et al. Study[6]

Time	Placebo-control Group (n = 22)	Lidocaine Group (n = 21)	P – value
2 hr post-operation	2.14 ± 1.73	2.57 ± 2.31	0.50

Bajracharya et al. (2019) also conducted a randomized, double-blind, control trial from January 2015 to April 2016 at BP Koirala Institute of Health Sciences.[7] A total of 90 patients, females 18-60 years old, met the criteria outlined in Table 1 and were enrolled into the study. On the day of surgery, the participants were randomized into two groups (esmolol and lidocaine) based on a computer-generated randomized number table.[7] Case numbers and the assigned treatment were sealed in opaque envelopes and solutions were prepared by the anesthesia staff. The attending anesthesiologist responsible for administering the appointed treatment was blind to the study as were the patients and investigator observing the outcomes.[7] Patients in the lidocaine group received a bolus of 1.5 mg/kg followed by an infusion at a rate of 1.5 mg/kg/h.[7] The patients designated to receive esmolol received an IV bolus (0.5 mg/kg) followed by an infusion which was titrated between 5 and 15 μg/kg/min, with a goal to keep the heart rate within 25% of the patient's baseline.[7] All patients received the same perioperative and postoperative management with the only difference being lidocaine vs. esmolol. At the end of the procedures, two patients from each group required conversion to an open cholecystectomy and were excluded from the data analysis.[7] Data was collected on the remaining 86 patients (43 from the lidocaine group and 43 from the esmolol group).[7]

Postoperative pain management consisted of 1 g of paracetamol and 30 mg of IV ketorolac at 6 and 8 hours for both groups.[7] Participants in this study were not given a PCIA pump. A mixed model analysis was used to analyze the data of this study and VAS pain scores were reported as means which can be seen below in Table 4. At 2 hours post-operation the median pain score for the lidocaine group was 1.8 and the median for the esmolol group was 1.6.[7] An individual p-value was not calculated for this specific time point. However, it was

determined that there was no significant difference between the pain scores of the esmolol group and lidocaine group at the completion of this study ($p = 0.38$).[7]

Table 4. Mean VAS Pain Scores for Lidocaine and Esmolol Groups at 2-hours Post-operation in the Bajracharya et al. study[7]

Time	Lidocaine Group (n = 43)	Esmolol Group (n = 43)
2-hr post-operation	1.8	1.6

DISCUSSION:

Perioperative intravenous (IV) lidocaine has shown to be beneficial at decreasing the postoperative pain scores of patients in larger abdominal procedures however, the benefit in less extensive procedures remains unclear. Out of the three studies included in this review, Song et al. (2017) was the only study that showed statistically significant data (lidocaine 3.01 ±0.65 vs. placebo 4.27 ±0.58, $p = 0.01$). Both Ortiz et al. (2016) and Bajracharya et al. (2019) determined that IV lidocaine is not a sufficient adjunct to traditional pain management treatments.[6,7]

The analgesic effects of lidocaine stem from its anti-inflammatory mechanism of action. The inflammatory reaction in laparoscopic surgery is far less than in major abdominal procedures.[5] This can be a potential reason why data is inconclusive for the objective of this review. However, researchers are hopeful that at the correct dose lidocaine will prove to be beneficial in smaller procedures. All three studies administered a 1.5 mg/kg bolus of IV lidocaine before the procedure began but did not use the same infusion rate of lidocaine. In the study by Song et al., an infusion rate of 2 mg/kg/h was administered whereas Ortiz et al. used a rate of 3 mg/kg/h and Bajracharya et al. infused at a rate of 1.5 mg/kg/h.[5,6,7] The inconsistency of the infusion rate between studies could have contributed to variations in the data.

The Bajracharya et al. study also used esmolol as a comparison rather than a placebo of normal saline. Esmolol belongs to the beta-blocker class and is typically used for its rate control effects and occasionally in the treatment of hypertension. In recent years, esmolol has gained popularity in the surgical field.[7] It has been shown to reduce postoperative pain because of its antinociceptive characteristics and has been used as an opioid sparing adjunct.[7] A potential reason as to why the data of this study was nonsignificant, is because the analgesic effects of esmolol and lidocaine are similar. Lidocaine succeeded at reducing postoperative pain but just was not superior to esmolol. Data for this study was also presented as a mixed model analysis. This caused the author of this review to subjectively determine the median pain score for both groups at 2 hours post-operation. Other scholars may have interpreted this data different, leaving room for error.

Another potential factor that could have contributed to the nonsignificant results of the Bajracharya et al. study is that it only included women. Previous studies have shown that women are more sensitive to pain and express more pain throughout their lives as well as after surgeries.[7] Thus, requiring more analgesic treatment.[7] This could have skewed the overall effects of lidocaine at reducing pain and does not represent the entire population that receives laparoscopic cholecystectomies.

The research for this review was limited by the author's search as well as characteristics of the studies themselves. PubMed and EBSCO: Academic Search Premier, Alt HealthWatch, AMED – The Allied and Complementary Medicine Database, and CINAHL Plus were the only databases utilized to select studies to answer the objective of this review. The use of only two databases as well as searching between the years of 2015-2020 could have excluded more accurate studies and better data. Limitations of the articles themselves include small sample size

and short postoperative monitoring. Patients in all three studies were only monitored and assessed in the PACU for 24 hours. It is possible that more significant results would have been found if their pain scores were recorded for a longer duration. A study by Koppert et al. showed that lidocaine had a major effect after 72 hours.[6] In addition, there was "no intention to treat" nor "worst case" analysis performed in any of the studies.

CONCLUSION:

This review has demonstrated that more research is needed to determine if perioperative lidocaine is a sufficient adjunct to traditional opioid therapy at decreasing postoperative pain scores following laparoscopic cholecystectomies. Song et al. found significant data that suggests lidocaine is effective as an adjunct in post-operative pain management.[5] However, Bajracharya et al. and Ortiz et al. found non-significant data.[6,7] Future research would benefit from including a larger sample size as well as using the same infusion rate of lidocaine. Using the same infusion rate would allow researchers to determine the full effect of lidocaine when compared to placebo and other analgesics. It would also be beneficial for future research to monitor patients' pain for a longer duration. This would ensure whether or not additional analgesics are needed for recovery or if lidocaine is sufficient alone. Despite the conflicting data of this review, there is evidence that lidocaine is able to reduce post-operative pain. The incidence of gallbladder disease will continue to increase and therefore, so will the number of laparoscopic cholecystectomies. It is important to continue research into new pain management techniques as millions of people will benefit.

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