Intraoperative Lidocaine Infusions for Postoperative Pain Management

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INTRAOPERATIVE LIDOCAINE INFUSIONS FOR POSTOPERATIVE PAIN MANAGEMENT

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An Independent Study
Submitted to the Graduate Faculty
of the
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Master of Science

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PERMISSION

Title  Intraoperative Lidocaine Infusions for Postoperative Pain Management

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ABSTRACT

**Title:** Intraoperative Lidocaine Infusions for Postoperative Pain Management

**Background:** It is known that postoperative pain is a significant cause for patient dissatisfaction following many types of surgery. Anesthesia professionals search for ways to treat pain from a multi-modal approach, however postoperative pain continues to be a surgical complication. Lidocaine infusions have been studied over the last two decades, and although literature has been controversial for certain surgical populations, research continues to advocate for its use in anesthesia. Lidocaine has been found to be a potent analgesic, anti-inflammatory, and anti-hyperalgesia medication that is safe and inexpensive. By reducing the use of opioids and incorporating lidocaine infusions into practice, patients can achieve better postoperative pain scores and avoid undesirable side effects such as respiratory depression, sedation, nausea, vomiting, constipation, and prolonged hospital stays.

**Purpose:** This independent study is meant to evaluate the current evidence regarding intraoperative lidocaine infusions. After a thorough review, the goal is to promote the use of lidocaine infusions to decrease postoperative pain scores, reduce the need for opioids, and increase patient satisfaction.

**Process:** A literature review was conducted using the electronic databases CINAHL and PubMed through the University of North Dakota Health Sciences Library. Additional studies in reference lists of meta-analyses and randomized controlled trials were also retrieved. Articles were only included in this literature search if they were published in 2010 or after.

**Results:** Intravenous lidocaine has been shown to decrease postoperative pain scores predominantly in patients undergoing abdominal surgery. Intravenous lidocaine infusions should
be considered a pharmacologic adjunct to achieve enhanced recovery after surgery and allow for
decreased use of opioids intraoperative and postoperative as well.

**Implications:** In particular surgical populations, utilizing lidocaine infusions intraoperatively
can reduce pain scores, decrease the use of postoperative opioids and acquired side effects, and
increase patient satisfaction. The findings are promising, but further research is indicated.

**Keywords:** lidocaine, pain, infusion, intraoperative
Intraoperative Lidocaine Infusions for Postoperative Pain Management

Background

Approximately 80% of patients undergoing a surgical procedure experience postoperative pain. Although a certain degree of pain is expected, less than half report adequate pain relief after surgery. Of those patients without adequate pain relief, 10 to 50% percent of patients will develop chronic pain (Academy of Integrative Pain Management, 2018). For anesthesia professionals, pain control intraoperatively and postoperatively is of high priority, but not always easy to accomplish. Traditionally, surgical pain has largely been treated with opioids, and although there is beneficial use for these medications in surgery, opioids also produce many unwanted side effects such as respiratory depression, nausea and vomiting, constipation, delirium, and sedation. Unfortunately, these side effects can lead to increased hospital length of stay, increased costs, and overall patient dissatisfaction.

Current research seeks to mitigate those unintended side effects through multi-modal analgesia and targeting various pain pathways and receptors with opioid sparing effects. Perioperative lidocaine infusions represent one piece of multi-modal anesthesia and have been shown to decrease pain in the post-surgical patient and decrease opioid requirements. Some studies have failed to demonstrate that lidocaine has any added benefit in treating postoperative pain in select surgical populations, however the purpose of this presentation is to highlight studies that offer strong evidence regarding lidocaine’s use as an analgesic adjunct. This analysis is meant to provide anesthesia professionals with a thorough review of intraoperative lidocaine infusions and evidence-based recommendations to enhance treatment of pain, improve surgical outcomes, and ultimately increase patient satisfaction.
Case Report

This case report involved a 43-year-old, 140 kg, 173 cm, Caucasian male patient who presented for an elective laparoscopic gastric bypass Roux-en-Y surgery. Past medical history was significant for obstructive sleep apnea (on home CPAP), asthma, hypertension, hyperlipidemia, gastric esophageal reflux disease, morbid obesity (BMI 46.5), and type 2 diabetes. Previous surgical history included laparoscopic adjustable gastric band surgery with removal, hernia repair, and hand surgery. Current home medications included budesonide-formoterol 160-4.5 mcg/puff inhaler used twice daily, hydrochlorothiazide 50 mg daily, losartan 100 mg daily, and a multivitamin daily. Current laboratory values were reported to be within normal limits with the exception of a mild increase of Hgb A1C at 6.3 and creatinine 1.16. Chest x-ray and EKG were normal.

Physical findings revealed a morbidly obese male who was assigned an ASA physical status class 3 primarily due to his body habitus. Vital signs were within normal limits. Cardiac exam was normal with a regular rhythm, no murmurs or rubs, breaths sounds were clear, and his mental status was alert and oriented. Pre-anesthetic evaluation included a Mallampati 3 airway, short neck with full neck range of motion, small mouth opening with adequate jaw protrusion, and no dental history. The patient was NPO for greater than 8 hours. Previous anesthesia records were reviewed and there was no history of previous airway management issues or anesthetic complications.

Preoperatively, a scopolamine patch and gabapentin 600 mg were administered. A 20-gauge peripheral IV was placed and an infusion of lactated ringers was initiated. The patient was transported to the operating room and placed supine on the operating table with a wedge ramp. Standard monitors consisting of 5-lead EKG, blood pressure, oxygen saturation, and end-tidal
CO2 detection sampling were applied. Pre-oxygenation was administered using 100% FiO2 via mask for approximately 5 minutes. General anesthesia was induced with intravenous midazolam 2 mg, fentanyl 100 mcg, lidocaine 140 mg, rocuronium 5 mg, propofol 250 mg, ketamine 30 mg, and succinylcholine 140 mg. The video laryngoscope was electively used because of his small mouth opening. A grade 1 view was obtained, and a size 8 endotracheal (ETT) was passed without difficulty. ETT placement was further verified using end-tidal CO2 monitoring and lung auscultation. Due to the patient’s asthma history, 3 puffs of albuterol were administered via the ETT after intubation. The patient was placed on volume control ventilation and general anesthesia was maintained with desflurane at 6% with a mixture of 1L/min oxygen and 1L/min air. A dexmedetomidine infusion was initiated after intubation with a bolus of 50 mcg over 10 minutes with a continuous infusion at 0.5 mcg/kg/hour. A continuous lidocaine infusion was added at 2 mg/min following induction but prior to incision. The patient also received magnesium 2 g, acetaminophen 1 g IV, enoxaparin 40 mg, and cefazolin 3 g prior to incision. No additional doses of narcotics were used intraoperatively.

Abdominal muscle relaxation was required, and multiple paralytic doses of rocuronium were given without effect. This warranted switching to cisatracurium 2 mg bolus doses, and adequate muscle relaxation was achieved. Intraoperatively, the patient required multiple doses of phenylephrine and ephedrine, and a phenylephrine infusion was started. The patient also received dexamethasone 4 mg after induction and ondansetron 4 mg at the end of the case. The lidocaine and dexmedetomidine infusions were stopped when the surgeon began closing the abdomen. The patient was fully reversed after surgical closure with glycopyrrolate 0.4 mg and neostigmine 5 mg. Ketorolac 30 mg was given prior to extubation. After paralytic reversal and spontaneous breathing effort on the ventilator, the patient was extubated 284 minutes after incisional cut time.
without difficulty. A nasal cannula was applied with 4 L oxygen, and the patient was transferred to the PACU. There was minimal EBL, and the patient received a total of 1800 ml of lactated ringers. In the recovery room, fentanyl 50 mcg was given twice for moderate pain, and a fentanyl PCA was initiated at 10 mcg/10min with no continuous rate. The patient was also started on scheduled ketorolac 30 mg every six hours.

Later that afternoon on the inpatient unit, the patient was found to be resting comfortably, pain rated at 4/10. The patient had been out of bed and walking to the bathroom. The patient’s vital signs were WNL, and patient was not SOB or in any acute distress. His abdomen was soft, distended, and slightly tender to palpation. According to the chart, on POD 1, the patient continued to rate his pain 4/10, reported to have slept well, was ambulating in the halls, passing gas, and his PCA had been discontinued. There had been no increase in his PCA rate. The patient remained on scheduled ketorolac and prn oxycodone and was discharged on POD 2.

**Literature Search**

**Method**

A literature search regarding intraoperative lidocaine infusions was performed through the University of North Dakota’s Health Science Library using the following terms: (lidocaine AND infusion AND pain AND intraoperative). Electronic databases included CINAHL and PubMed. When using the above keywords, 15 articles were found in CINAHL. In PubMed, lidocaine was entered into the MESH database, the same keywords were added to the search, and 23 articles were found in PubMed. Of those articles, 8 articles were used in this literature review. Additional studies were retrieved from reference lists of meta-analyses and randomized controlled trials. The literature search of randomized control trials and meta-analyses was limited to 2012 to the present date.
Discussion

Pain Pathway

In order to understand the role of local anesthetics in pain management, it is imperative to dive into the elements of the pain pathway. The International Association for the Study of Pain (IASP) defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (2018). The first stage of the pain pathway involves pain transduction, which occurs when a noxious stimulus is transformed into an action potential. This occurs when specialized sensory receptors, called nociceptors, respond to noxious stimuli and an electrical impulse is generated. Nociceptors are found on A-delta and C nerve fibers, meaning they are the primary nerve fibers that are responsible for conducting pain to the brain. These nerve fibers are distributed in skin, viscera, muscles, joints, and meninges (Reddi & Curran, 2013). A-delta nerve fibers have a large diameter, are lightly myelinated and conduct nerve impulses rapidly, while C fibers have a smaller diameter, are unmyelinated, conduct nerve impulses slowly, and innervate visceral internal organs (Nagelhout & Elisha, 2018). When a noxious stimulus is sensed, it causes a release of chemical mediators and neurotransmitters such as substance P, glutamate, bradykinin, histamine, serotonin, prostaglandins, and cytokines. These mediators and neurotransmitters directly stimulate peripheral nociceptors and cause an influx of sodium ions to enter the nerve fiber membrane and create depolarization. This creates an action potential and pain is generated (Nagelhout & Elisha, 2018). Once the action potential is generated, it is carried from the periphery to the central nervous system. Local anesthetics take effect at the beginning of the pain pathway and prevent the conversion of noxious stimuli into an action potential. In this way, the sensory input cannot be transmitted to the brain, and consequently analgesia occurs (Nagelhout & Elisha, 2018).
The second stage of the pain pathway involves pain transmission. The spinothalamic track is a pathway that transports pain signals from the trunk and lower body via the first, second, and third-order neurons. Primary afferent neurons are responsible for detecting noxious stimuli and moving the sensory input from the nociceptors to the gray matter of the dorsal horn in the spinal cord. The dorsal horn can be divided into ten layers called Rexed Laminae. A-delta and C fibers transfer information in Rexed lamina 1 and 2, in addition to projections to other laminae. First and second-order neurons connect in the dorsal horn, and second order neurons are responsible for transmitting pain signals from the spinal cord to the brainstem in the contralateral spinothalamic tract. Third order neurons conduct pain impulses from the brain stem to the thalamus, cortex, and higher levels of the brain and terminate in the somatosensory cortex where the perception of pain occurs. Third order neurons also have an important role in the descending inhibitory pain pathway (Reddi & Curran, 2013). There is a synaptic cleft between the ends of nerve fibers and the dorsal horn neurons. Excitatory neurotransmitters such as glutamate, substance P, bradykinin, and nitrous oxide are released to transmit the pain impulses across the synaptic cleft. Then the pain signals are transmitted from the spinal cord to the brain stem and thalamus via the spinothalamic pathway. The third stage of the pain pathway occurs when pain impulses reach the thalamus and pain is processed (Kumar, Gupta, Kaleem, & Pandey, 2014).

The fourth stage in the pain pathway involves pain modulation. Modulation involves altering neural afferent activity such as pain inhibition or enhancing of the pain signal. Pain is altered along the descending pain pathway in the location of the periaqueductal grey (PAG) in the midbrain (Reddi & Curran, 2013). The PAG contains a high concentration of endogenous opioids and other inhibitory neurotransmitters such as serotonin, acetylcholine, and oxytocin.
which serve as a natural way to “turn off” pain (Kumar, Gupta, Kaleem, & Pandey, 2014). Many analgesia pharmaceuticals such as opioids occur at this component of the pain pathway.

**Lidocaine**

**Mechanism of Action**

After reviewing the physiology of the pain pathway, lidocaine’s mechanism of action can be delineated. Intravenous lidocaine is known to have analgesic, anti-inflammatory, and anti-hyperalgesia properties, but its role in pain begins at the cellular level. Lidocaine produces analgesia through the involvement of sodium channel blockade, acetylcholine in cerebral spinal fluid, NMDA receptors, and by reducing inflammatory responses. Lidocaine contains an aromatic ring with an amine at opposite ends of the molecule and is separated by a hydrocarbon chain and an amide bond. This amide bond structure classifies lidocaine as an amide local anesthetic. Lidocaine’s primary mechanism of action involves binding to the peripheral and central voltage gated sodium channel’s inner core of the alpha subunit (NYSORA, 2019a).

Sodium channels help maintain an electrical gradient across the neuronal cell membrane, initiate and facilitate action potentials, and are required for transmission of peripheral nociceptive stimuli to reach the brain. Sodium channels can exist in “resting,” “open,” and “inactivated,” states, and supply both skeletal and cardiac muscle and neuronal tissue. At rest, sodium channels are in the closed state, and sodium ions are highly concentrated in the extracellular space. When an action potential occurs, neuronal sodium channels quickly open which allows extracellular sodium to enter the cell, making the inside of the cell positive and depolarization occurs (NYSORA, 2019a). Anesthesia occurs when lidocaine (along with all local anesthetics) binds to sodium channels, prevents the sodium influx and action potential, and
results in conduction blockade and a selective depression of pain transmission in the spinal cord so the brain cannot sense painful stimuli (Yon et al., 2013 & Peng et al., 2016).

When lidocaine is administered intravenously, it also increases the amount of acetylcholine in the cerebrospinal fluid. This increase in acetylcholine inhibits the descending pain pathway resulting in analgesia. It is thought that lidocaine contributes to a release of endogenous opioids and an inhibition of the excitatory neurotransmitter glycine (Ibrahim, Aly, & Farrag, 2018).

Lastly, lidocaine has potent anti-inflammatory effects by inhibiting the N-methyl-d-aspartate (NDMA) receptor. Noxious events, such as surgery, create hyperexcitability in the NMDA receptors and the release of cytokines in the central nervous system. When lidocaine blocks NMDA receptors, there is an inhibition of inflammatory mediators and a decrease in the post-synaptic depolarization which results in decrease of pain signaling to the brain. When lidocaine can reduce cytokine production, there is a decreased inflammatory response, less windup of pain, and a decreased risk for hyperalgesia (Ibrahim, Aly, & Farrag, 2018). Additionally, when lidocaine reduces the inflammatory processes in the bowel by inhibiting cytokine secretion, there is a more rapid return of bowel function on top of decreased pain.

Along with lidocaine’s unique role in pain, it also has a short half-life and favorable safety profile compared to esters, which makes it the local anesthetic of choice for intravenous administration. Lidocaine has a rapid onset of approximately 45-90 seconds, and the initial half-life for bolus administration is approximately 10 minutes due to rapid liver metabolism and redistribution (Gordon & Schroeder, 2008). When lidocaine infusions are discontinued, plasma levels decrease quickly. With a continuous infusion, the half-life is estimated to be about 1.5 to 2 hours, and in healthy patients there is no drug accumulation (Eipe, Gupta, & Penning, 2016).
Lidocaine is metabolized in the liver and clearance is highly dependent on hepatic blood flow and enzyme function. Lidocaine should be used with caution in patients with decreased hepatic blood flow, such as in heart or liver failure or patients taking cytochrome inhibitor medications. Likewise, renal failure increases volume of distribution of amide local anesthetics and can increase metabolic by-products (NYSORA, 2019a). Ultimately, dosages should be reduced by 50% in patients older than 70 years of age or with liver disease, in order to avoid complications such as CNS depression, seizures, drowsiness, bradycardia, and hypotension (Gordon & Schroeder, 2008).

**Side Effects**

Although side effects from a lidocaine infusion have been shown to be of low risk, it remains vital for anesthesia practitioners to be aware of complications and signs of toxicity. Mild symptoms, often associated with low lidocaine plasma concentrations, consist of restlessness, tinnitus, circumoral numbness, vertigo, or tremors. More serious side effects include drowsiness, hypotension and tachycardia, and can progress to bradycardia, arrhythmias, seizures, unconsciousness, coma, and cardiovascular collapse. According to NYSORA, “most local anesthetics will not cause cardiovascular toxicity until the blood concentration exceeds three times that necessary to produce seizures” (2019b).

**Intraoperative Use of Lidocaine**

Benefits from intraoperative lidocaine infusions have been controversial, however there has always been success reported in the abdominal surgical population. The first study involves a prospective, double-blind, placebo-controlled trial using 36 patients undergoing subtotal gastrectomies who received a lidocaine infusion with a bolus dose of 1.5 mg/kg followed by a continuous infusion of 2 mg/kg/hour. The study showed that these patients had lower pain scores
24 hours after surgery, and fentanyl consumption was significantly lower in this group until 12 hours postoperatively compared to a normal saline placebo infusion. No differences were found related to nausea or hospital length of stay (Yon, Choi, Kang, Park & Yang, 2013). Two years later, another randomized, double-blind, placebo-controlled study was conducted. This study included 50 patients undergoing scheduled laparoscopic colectomies and found similar results. The same lidocaine dose was used as above, and again, patients in the lidocaine group reported significantly lower pain scores 24 hours postoperatively and required significantly less fentanyl until 12 hours after surgery compared to a normal saline placebo group. Patients receiving lidocaine infusions in this study also had fewer complaints of nausea and higher recovery satisfaction scores (Ahn et al., 2015). In both studies, patients in the lidocaine groups were found to have lower C-reactive protein levels postoperatively signifying that lidocaine possesses anti-inflammatory properties. It is also important to note that none of the patients in either the lidocaine or placebo group received pre-medications or any additional analgesics intraoperatively other than lidocaine (Ahn et al., 2015 & Yon et al., 2013).

The use of intraoperative lidocaine has also been studied in patients undergoing bariatric surgery. A prospective randomized, double-blind, placebo-controlled clinical trial consisting of 50 patients undergoing laparoscopic bariatric surgery was reviewed. The study found that when an intraoperative lidocaine infusion was used with a bolus of 1.5 mg/kg followed by a 2 mg/kg/hour infusion, patients reported higher postoperative quality of recovery scores, had lower postoperative opioid requirements, and fewer complaints of nausea when compared to a normal saline placebo group. Patients in both groups were pre-medicated with 0.04 mg/kg IV midazolam and given propofol 1-2 mg/kg, remifentanil 0.1 mcg/kg/min IV infusion, and succinylcholine 1-2 mg/kg for induction. Anesthesia maintenance was controlled with remifentanil titrated to 20% of
blood pressure baseline with desflurane titrated to a BIS of 40-60, and rocuronium. When laparoscopic instruments were removed, hydromorphone 0.01 mg/kg was given. Multi-modal analgesic techniques may be most important in this morbidly obese patient population because opioids are often accompanied by adverse respiratory complications such as hypoventilation and hypoxemia which can complicate postoperative recovery (De Oliveira Jr. et al., 2013).

Multiple randomized controlled trials have also discovered the significant impact intravenous lidocaine infusions have on laparoscopic cholecystectomy patients. A randomized, blinded, placebo-controlled trial of 71 patients concluded that when using a lidocaine bolus of 1.5 mg/kg before skin incision followed by an infusion of 2 mg/kg/hour, patients in the lidocaine group reported significantly lower pain scores compared to the normal saline placebo group at 2 hours and 6 hours postoperatively. Additionally, participants in the lidocaine group had significantly longer times for the request of the first dose of analgesic compared to the normal saline group, and the total mean analgesic requirements after surgery were significantly less. This study also found that times to first flatus and bowel movement were significantly shorter in patients who received lidocaine. This is noteworthy considering abdominal surgery patients often have complications such as ileus, nausea, vomiting, and constipation. This particular study also measured concentrations of inflammatory markers such as serum IL-6, IL-8, IL-1ra before induction of anesthesia, at the end of surgery, and at 12 hours postoperatively. It was found that the levels of serum IL-6 and IL-8 in the lidocaine group at the end of surgery and 12 hours postoperatively were lower than the control group, reaffirming that lidocaine exhibits an anti-inflammatory quality which could be responsible for the decreased times for return of bowel function (Song, Sun, Zhang, Li, & Yang, 2017).
A meta-analysis of 5 randomized controlled trials involving 274 patients was conducted on patients undergoing laparoscopic cholecystectomies who also received intravenous infusions of lidocaine for pain management. Of the 5 reviewed trials, 4 trials used a lidocaine bolus of 1.5 mg/kg followed by a continuous infusion of 2 mg/kg/hour, and 1 trial used a lidocaine bolus of 1.5 mg/kg but increased the continuous rate to 3 mg/kg/hour. The meta-analysis found that the lidocaine infusion group had significantly lower pain scores at 12 hours, 24 hours, and 48 hours after surgery. Patients in the lidocaine group were also found to have reduced opioid consumption and fewer adverse effects (Zhao et al., 2018).

Lastly, a double-blind, placebo-controlled study with 45 participants found that when using a lidocaine bolus of 1 mg/kg on induction followed by a 2 mg/kg/hour infusion for patients undergoing laparoscopic gynecological procedures, patients had decreased analgesic requirements, but the trial failed to achieve statistical significance when compared to the normal saline placebo group. However, the patients receiving lidocaine has a significantly decreased time to first flatus (Grady, Clark, Lenahan, Oudekerk, Hawkins, Nezat, Pellegrini, 2012). This is one of the few studies that utilized a lidocaine bolus of only 1 mg/kg, and it must be questioned if this decrease in bolus dose could possibly affect outcomes.

There is substantial evidence that supports the use of lidocaine infusions to decrease postoperative pain in patients with abdominal surgeries, and other surgical populations have also experienced positive effects. Intraoperative lidocaine has also proved to be effective in patient populations undergoing spinal fusion surgery, supratentorial brain tumor surgery, laminectomy/discectomy, and mastectomies. A recent prospective, randomized, double-blinded study involving a total of 40 patients undergoing spinal fusion surgery demonstrated that administering a lidocaine bolus of 2 mg/kg before induction followed by a continuous rate of 3
mg/kg/hour until the end of surgery reduced the postoperative pain scores for up to 3 months, reduced morphine consumption in the first 24 hours postoperative, and prolonged the time to first request for additional pain medication compared to a normal saline placebo group. In this study, all participants received an anesthesia regimen of propofol, Cisatracurium, isoflurane, ketorolac, fentanyl, and acetaminophen in equal doses (Ibrahim, Aly, & Farraq, 2018).

In patients having supratentorial brain tumor surgery, it was found that lidocaine significantly decreased the proportion of patients with acute pain in the PACU. A prospective, randomized, double-blinded study with 80 patients found that when using an intraoperative lidocaine with a bolus of 1.5 mg/kg after induction and an infusion of 2 mg/kg/hour until the end of surgery, the incidence of “no pain” was higher in the lidocaine group than the normal saline placebo group prior to transferring out of the PACU. There were no patients with moderate or severe pain in either group Anesthesia between the groups also consisted of using midazolam 0.05 mg/kg for premedication followed by Sufentanil 0.2 mcg/kg, propofol 1.5-2.5 mg/kg, and rocuronium 0.6 mg/kg for induction. Anesthesia was maintained using propofol, sevoflurane, and a remifentanil infusion (Peng et al., 2016). Opioid sparing effects in this neuro-surgical population are even more important as surgeons often require neurological assessments immediately after surgery.

Lidocaine has also been shown to decrease pain and reduce the consumption of opioids in patients undergoing laminectomy and discectomy lumbar surgery. A prospective, randomized, double-blinded, and placebo-controlled clinical trial using 51 subjects agreed that lidocaine infusions contribute to decreased postoperative pain scores, reduced fentanyl consumption, and decreased length of stay when compared to a normal saline placebo group. The lidocaine bolus was given at 1.5 mg/kg and the infusion was dosed at 2 mg/kg/hour until the end of surgery. The
2 groups received the same anesthetic protocol, which consisted of thiopental 5 mg/kg and rocuronium 0.6 mg/kg for induction. Anesthesia was maintained using 2 to 3% sevoflurane with 1.5 L/min nitrous oxide and 1.5 L/min O2 mixture. No premedications were given. There is no note of any opioids or other analgesics being administered intraoperatively. The lidocaine group reported less pain than the normal saline group for up to 48 hours, and the patients also had a decreased hospital length of stay (Kim et al., 2014).

Lastly, lidocaine infusions have been shown to improve postoperative quality of recovery, reduce intraoperative opioid requirements, and improve chronic pain for patients undergoing mastectomy for breast cancer. A prospective, double-blind, randomized clinical trial using 116 female patients utilized a lidocaine bolus of 2 mg/kg after induction followed by an infusion of 2 mg/kg/hour. The study compared intraoperative lidocaine, magnesium, and normal saline groups. Magnesium is being incorporated into anesthesia as another multi-modal technique because it is also a NMDA receptor antagonist and has anti-nociception mechanisms. The intraoperative magnesium was initiated with a bolus of 20 mg/kg followed with a continuous infusion of 20 mg/kg/hour. The intraoperative lidocaine group had favorable effects on early postoperative recovery and higher quality of recovery scores when compared to the magnesium and normal saline groups. The quality of recovery survey included dimensions such as physical comfort, emotional state, physical independence, psychological support, and pain. The study also showed that lidocaine and magnesium did not have significant differences in reducing intraoperative opioid consumption, but they both proved superior to normal saline infusions (Kim et al., 2017).

While many reputable trials appear to decrease postoperative pain scores and reduce opioid requirements, lidocaine’s use in other surgical procedures can be controversial. Each
surgery possesses a different level of triggered pain and may alter the effects of lidocaine. Although the previously mentioned study argues that lidocaine infusions can be effective for mastectomy patients, a study published in the same year disagrees. In this particular trial, it was found that there were no differences in quality of recovery, pain scores, or opioid consumption for mastectomy patients at periods of 24 hours post operation up to 6 months. The study examined 148 patients who were randomly divided into 2 groups. One group received 1.5 mg/kg bolus of IV lidocaine followed by an infusion of 2 mg/kg/hour, and the placebo group received a normal saline bolus and infusion at the same rates. Each group received identical anesthetic regimens of propofol, sevoflurane, remifentanil infusions, and hydromorphone at the end of surgery. It was found that pain burden, opioid consumption, and quality of recovery were no different at 24 hours postoperative when comparing the lidocaine and normal saline groups (Kendall et al., 2017). Although this study includes recent data, all surgical study participants received intraoperative opioid medications which could affect the validity of the study when compared to studies that do not use any additional opioids. One must question whether the lidocaine infusion would show any benefit when compared to normal saline if the patient is already well narcotized.

Another study argued that lidocaine infusions are not effective for mastectomy patients. A 2016 meta-analysis of randomized control trials found that lidocaine infusions did not affect postoperative pain scores at rest or activity 2 hours to 3 days when compared to a placebo of normal saline. However, at 72 hours postoperative, the lidocaine group required fewer analgesics. There was also a trend of lower pain scores in the lidocaine group at 2 hours postoperative and 48 hours, but the evidence was not statistically significant. The meta-analysis included a total of 84 patients randomized to the lidocaine group, and 83 patients randomized to
the placebo group. The study concluded that lidocaine may produce more significant benefits in patients undergoing abdominal surgery because the intensity of pain is higher than many other surgeries that have been studied (Chang et al., 2016).

When comparing all of the above studies to the patient in the case report, it was found that the majority of studies used a lidocaine bolus of 1.5 mg/kg followed by a continuous infusion of 2 mg/kg/hour. The case report patient received a lidocaine bolus of 1 mg/kg during induction followed by a continuous infusion of 2 mg/min, which was not weight based and underdosed based on the patient’s body weight. In addition to a lidocaine infusion, the case report patient also received preoperative acetaminophen and gabapentin and other multi-modal agents in surgery including ketamine, magnesium, a dexmedetomidine infusion, and ketorolac, which all could have contributed to his recovery. Many reviewed studies did not include other multi-modal medications when testing the efficacy of lidocaine. Like the studies regarding abdominal surgery, the case report patient had well controlled pain and limited narcotic use postoperatively. Additionally, the case report patient did not have preoperative or postoperative C-reactive protein levels drawn so the inflammatory response could not be assessed.

Even though most studies used a consistent lidocaine dose, many studies were vague regarding when the lidocaine bolus was started, how long the bolus infused, and precise times for infusion discontinuation which could affect outcomes. In most studies, it was standard for postoperative patients to receive a narcotic PCA. Although this may seem counterintuitive, only demand dosing was ordered and significantly less total narcotic PCA was required in the lidocaine groups (Ahn et al., 2015, De Oliveira Jr. et al., 2013, Kim et al., 2014, Peng et al., 2016, & Yon et al., 2013). Most studies assessed patients’ pain using a Visual Analog Scale (VAS) with 0 meaning “no pain” and 10 meaning the “worst possible pain”. Pain was evaluated
at slightly different intervals, but common times included 0, 2, 4, 8, 12, 24, and up to 48 hours post-surgery. Most studies collected data regarding lidocaine’s effect on postoperative pain scores, time until request for first pain medication, and total opioid dosing postoperatively (Ahn et al., 2015, De Oliveira Jr. et al., 2013, Khan et al., 2016, Kim et al., 2014, Kim et al., 2017, Peng et al., & Yon et al., 2013).

One inconsistency that was noted while reviewing the literature was that studies failed to describe whether lidocaine should be dosed per total body weight, ideal body weight, or adjusted body weight. For the patient in the case report, total body weight was used for dosing. A lidocaine bolus of 140 mg was given but only a 1 mg/kg calculation was used. The patient received a continuous lidocaine infusion at 2 mg/min (120 mg/hour) instead of the recommended 2 mg/kg/hour. If 2 mg/kg/hour would have been used and based on TBW, the continuous dose would have increased from 120 mg/hour to 280 mg per hour. A dose of 2 mg/min would underdose a patient as long as they weigh over 60 kg. De Oliveira Jr. et al. (2013) is the only study that advises using adjusted body weight (ABW) for dosing lidocaine infusions. The calculation is \[ \text{ideal body weight (IBW) + 0.4 x (actual body weight- IBW)} \]. This is an important consideration when dosing lidocaine infusions because a dose based on TBW can easily be doubled compared to IBW, especially for obese patients.

**Maximum Safe Doses**

In order to safety administer intravenous lidocaine infusions, it is imperative anesthesia professionals understand how to calculate maximum dosages for lidocaine infusions and other possible local anesthetics used by the surgeon. The maximum dose for plain lidocaine is 4 mg/kg and increases to 7 mg/kg if epinephrine is added. It is important to remember that the overall maximum dose for lidocaine is 300 mg, even if the dose per kilogram exceeds this. The
maximum dose is also calculated as a “per hour” guideline, which means each hour an additional 300 mg can be given safely. For example, if the patient is 75 kg and a bolus of 1.5 mg/kg (112.5 mg) and infusion of 2 mg/kg/hour (150 mg) is used, theoretically the patient would receive 262.5 mg after the first hour. The lidocaine bolus is often given during induction and takes the place of a bolus given to relieve propofol induced pain or to blunt the SNS response of airway manipulation with intubation. After the first hour, a continuous infusion rate of 2 mg/kg/hour would equal 150 mg for this patient of 75 kg. This would mean the patient is receiving 50% of the local anesthetic maximum dose, therefore the surgeon is able to use 50% of the maximum dose of local anesthetic for skin infiltration at the end of surgery. For example, if the surgeon injects 0.25% bupivacaine with epinephrine during incision closure, the maximum dose is 3 mg/kg. The patient's calculated max dose for bupivacaine is 225 mg, and 50% of that is 112.5 mg.

In order to calculate the amount in milliliters, the dose must be divided by the local anesthetic concentration. If the local anesthetic is 0.25% bupivacaine, 45 ml can still be injected safely. Additionally, when calculating maximum doses, it can be theorized that a continuous infusion is constantly being metabolized at a steady rate, meaning at the end of each hour, not all of the local anesthetic is adding up at one time.

In some cases, local anesthetics can reach their maximum doses quickly which poses a greater risk for lidocaine toxicity, however none of the articles found evidence to support this fear. Specifically, authors noted that no blood samples showed toxic levels and no cardiovascular or neurological adverse events occurred (Ahn et al., 2015, De Oliveira Jr. et al., 2013, & Peng et al., 2016). Lidocaine toxicity is likely to be seen at plasma concentration of 5 mcg/ml. However, when a bolus of 1-2 mg/kg is administered and then followed with a continuous infusion of 1.5 mg/kg, the corresponding plasma concentration is only at 2 mcg/ml, and the risk of toxicity is
low (Lauretti, 2008). In this way, practitioners need to be aware of lidocaine toxicity, risks, and treatment, however, lidocaine infusions have a favorable safety profile and should not be avoided because of the fear of overdosing.

Although reaching critical levels with lidocaine infusions is rare, it remains imperative for anesthesia professionals to be aware of local anesthetic systemic toxicity (LAST) and treatment options. Variables that increase the risk of LAST include using the wrong local anesthetic drug or dosage, extremes of age, patient comorbidities, small muscle mass, liver or kidney failure, and malnutrition. Side effects of local anesthetics and more serious signs of LAST are mentioned previously. In terms of LAST, prevention is key. It is imperative to know maximum safe doses, use proper monitoring, careful selection of local anesthetic and attention to concentration, and have adequate preparation for possible resuscitation (Nagelhout & Elisha, 2018).

Treatment of LAST involves the need for immediate recognition followed by seizure management, advanced cardiac life support (ACLS) and prompt administration of 20% lipid emulsion. The local anesthetic should be stopped, and one should seek help. Benzodiazepines are the first line treatment for seizure activity. If patients are unstable, airway management and circulatory support is required (NYSORA, 2019b). Reversal of LAST is treated with lipid emulsion and CV collapse will occur if lipids are not administered. If the patient weighs greater than 70 kg, a 20% lipid emulsion bolus of 100 ml bolus is given over 2-3 minutes followed by an infusion of 200-250 ml over 15-20 minutes. If patients remain unstable, bolus doses can be repeated twice, and infusion rates can be doubled. If the patient weighs less than 70 kg, a bolus dose of 1.5 mg/kg is given followed by an infusion of 0.25 ml/kg/min until symptoms resolve. There is a dosing limit of 12 ml/kg which is particularly important in the small child. After a
LAST incident, patients should be continuously monitored 4-6 hours after a cardiovascular event or at least 2 hours after a CNS event. There is a LAST algorithm that should be available and familiar to anesthesia providers who administer local anesthetics (American Society of Regional Anesthesia and Pain Medicine, 2018).

**Practice Recommendations**

After completing a thorough literature review, there are two main practice recommendations. First, anesthesia professionals should consider the use of lidocaine infusions with a bolus and continuous infusion for any abdominal surgery. According to the most current literature, the recommended intravenous infusion should include an initial bolus of 1.5 mg/kg followed by an infusion of 2 mg/kg/hour (Zhao et al, 2018). The lidocaine infusion bolus should be initiated immediately prior to induction and followed by a continuous infusion until wound closure. A bolus is always recommended because a continuous infusion alone will take 4-8 hours to achieve steady state plasma concentration which is often much longer than common surgical times (Eipe, Gupta, & Penning, 2016). Other opioids can be used intraoperatively and postoperatively, but practitioners may find that less opioids are required. Lidocaine infusions should be predominantly considered for patients undergoing abdominal surgery because data is most consistent with this specific population. Additionally, the infusions should be reserved for cases greater than one hour where larger amounts of opioids are generally needed.

The second, and possibly most important recommendation, includes the need for further research in many areas. Additional high-quality studies need to be performed with larger sample sizes in order to continue to validate the current use of lidocaine. Further studies need to include comparisons regarding different lidocaine doses and timing of initiation and discontinuation of the infusion. Although most randomized controlled trials utilized a lidocaine bolus of 1.5 mg/kg
followed by a continuous infusion of 2 mg/kg/hour, the optimal perioperative treatment protocol is unknown. Lastly, there also needs to be further research conducted regarding dosing on TBW compared to IBW or ABW as a way to mitigate unnecessary side effects.

**Conclusion**

Pain is complex and an unwanted component of almost all surgical procedures. Intraoperative lidocaine administration should strongly be considered when formulating a multimodal approach to pain management within an anesthetic plan. Intraoperative lidocaine has proven to be a safe, valuable, and a cost-effective intervention that can decrease postoperative pain, reduce the use of opioids, and increase overall patient satisfaction.
References


NYSORA. (2019a). Clinical pharmacology of local anesthetics. Retrieved from

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Appendix

Intraoperative Lidocaine Infusions for Postoperative Pain Management
Sarah Solberg, SRNA

Introduction
- Postoperative pain is a significant cause of patient dissatisfaction following surgery
- Multi-modal anesthesia can...
  - Decrease the need for opioids
  - Help mitigate unwanted side effects of opioids
  - Decrease postoperative pain
- Lidocaine infusions can provide analgesic, anti-inflammatory, and anti-hyperalgesia benefits

Case Information
- 43 years old, male
- 146 kg, 173 cm, BMI 48.5
- ASA 3
- Elective gastric bypass Roux-en-Y
- PMH: COPD, asthma, HTN, HLD, GERD, obesity, DM type 2

Pre-operative Evaluation
- Past Surgical History
  - Laparoscopic adjustable gastric band surgery with removal
  - Hernia repair
  - Head surgery
- Airway evaluation
  - Moderately obese
  - Small incision opening
  - Short neck
  - Mallampati 3
  - No dental history
- Vitals, labs, chest x-ray, and EKG normal

Anesthetic Course
- Pre-op Meds
  - Nicoprostolamine patch
  - Gabapentin 600 mg
- Induction
  - Midazolam 2 mg
  - Fentanyl 100 mcg
  - Lidocaine 140 mg
  - Rocuronium 5 mg
  - Propofol 20 mg
  - Risperidone 10 mg
  - Succinylcholine 140 mg
- RSI due to possible difficult airway
- Video laryngoscope electrocautery used
- Tolerated volume control ventilation

Anesthetic Course
- Maintenance
  - Desflurane at 6%
  - Dexamethasone 50 mg bolus with 0.5 mcg/kg/hour
  - Lidocaine infusion started at 2 mg/min prior to incision, bolus given with induction
  - Magnesium 2 g
  - Acetaminophen 1 g IV
  - Multiple doses of rocuronium, switched to vecuronium
  - Multiple doses of phentolamine and ephedrine.
INTRAOPERATIVE LIDOCAINE INFUSIONS

**Anesthetic Course**

- **Emergence**
  - No intraoperative issues
  - Lidocaine and doxmedetomidine infusions stopped during abdominal closure
  - Glycopyrrolate 0.4 mg
  - Nectosome 5 mg
  - Ketorolac 30 mg
- Pi extubated 284 minutes after incisional cut time
- **NO ADDITIONAL NARCOTICS USED INTRAOPERATIVELY**

**PACU**

- **PACU**
  - Uncomplicated
  - Pi received Fentanyl 50 mcg twice for mild-moderate pain
  - Standard Fentanyl PCA started with bolus dosing only
  - (10 mcg every 10 minutes)
  - Pi started on scheduled ketorolac 6 hrs
- **Inpatient Unit**
  - Rested comfortably out of bed, walking to bathroom
  - Pain 4/10
  - PCA discontinued on POD #1, given oxycodone 5mg at the time of PCA discontinuation

**Discussion**

- **Pain Pathway and Lidocaine**
  - MOA
    - Works at the transmission phase of the pain pathway
    - Via sodium channel blockade
    - No further depolarization
    - Pain transmission is selectively depressed
    - Anti-inflammatory response
    - Blockade of NMDA receptors

**Favorable Effects of Lidocaine**

- **Short half-life**
  - 10 minutes for bolus
  - 1.5 to 2 hours for infusion
- **Safe**
- **Rapid onset**
- **Metabolized in the liver.**
- **Clearance is dependent on hepatic blood flow and hepatic enzyme function**

**Evidence Regarding Lidocaine Infusions**

- **Gastrectomy and Colectomy Surgical Patients**
  - Lidocaine bolus of 1.5 mg/kg followed by a continuous infusion of 2 mg/kg/hr compared to a normal saline group
  - Patients in the lidocaine group reported
    - Lower pain scores 24 hours after surgery
    - Decreased consumption of fentanyl
    - Lower C-reactive protein levels postoperatively

- **Gastric Bypass Surgical Patients**
  - Lidocaine bolus of 1.5 mg/kg followed by a continuous infusion of 2 mg/kg/hr compared to a normal saline group
  - Patients in the lidocaine group reported
    - Higher postop weight scores
    - Lower post-op opioid requirements
    - Fewer complaints of nausea

*(Ref: Chiu et al., 2015; Yoon et al., 2013)*
Evidence Regarding Lidocaine Infusions

- **Laparoscopic Cholecystectomy Surgical Patients**
  - Lidocaine bolus of 1.5 mg/kg followed by a continuous infusion of 2 mg/kg/hr compared to a normal saline group
  - Patients in the lidocaine group reported
    - Significantly less pain
    - Longer times for the removal of the first dose of analgesic
    - Less total analgesic requirements after surgery
    - Shorter times to post-op time to first fluid and first BM
    - Lower post-op levels of serum 1.6 and 2

(Onn, Onn, Zhang, Li, & Yang, 2017; Zhao et al., 2018)

Controversial Studies

- **Mastectomy Surgical Patients**
  - Kendall et al., 2017
    - Lidocaine bolus of 1.5 mg/kg with infusion of 0.4 mg/kg/hr
    - Pain burden, opioid consumption, and quality of recovery scores were no different at 24 hrs postop
  - Chang et al., 2016
    - No difference in post-op pain scores at rest or activity 2 hrs to 3 days. However, at 72 hrs post-op, the lidocaine group received fewer analgesics

Comparing Evidence with Case Report

- **Current Evidence**
  - Lidocaine bolus of 1.5 mg/kg
  - Weight-based continuous lidocaine infusion of 2 mg/kg/hr
  - Many studies did not administer preoperative or use multi-modal analgesics

- **Case Report**
  - Lidocaine bolus of 1 mg/kg
  - Continuous lidocaine infusion of 2 mg/kg/hr
  - Patient received preoperative grids and multi-modal analgesics such as ketorolac, demerol, and magnesium

Understanding Lidocaine Max Doses

- Max dose of plain lidocaine: 4 mg/kg
- Overall max dose: 300 mg
- Theoretically, max dose is PER HOUR and pertain more to bolus doses
  - Infusions are constantly being metabolized minute by minute
- 75 kg patient
  - Bolus of 1.5 mg/kg = 112.5 mg
  - Infusion of 2 mg/kg/hr = 150 mg/hr
  - Total of 262.5 mg in the first hour

Calculating Lidocaine Doses

- Anesthesia providers need to share the max dose with the surgeon’s use of lidocaine
  - Lidocaine infusion total of 150 mg/hr is 50% of max dose (300 mg)
  - The surgeon is able to use 50% of the max dose of local anesthetic for incisional closure, etc.
    - Incision closure with fentanyl max dose is 4 mg/kg
    - 75 kg x 4 = 300 mg
    - 50% of 300 is 150 mg
    - 112.5 / 2.5 (melt) = 45 ml of local can be used

LAST

- Signs/symptoms
  - Hypotension
  - Tachycardia
  - Gastrointestinal motility
  - Vertigo
  - Discontinue LOC
  - Seizures and hypoventilation → bradycardia
  - Arrhythmia
  - Nausea
  - Unconsciousness
  - Coma
  - CV collapse
INTRAOPERATIVE LIDOCAINE INFUSIONS

LAST
- Treatment
  - Stop administration of local anesthetics
  - Benzodiazepines for seizures
  - Airway and circulatory support
- If <70 kg, bolus 20% lipid emulsion @ 1.5 mg/kg followed by an infusion of 0.25 mg/kg/hr
- If >70 kg, bolus 20% lipid emulsion 100 ml followed by an infusion of 200-250 ml over 15-20 min
- Patients should be continuously monitored after LAST event

Recommendations
- Consider using lidocaine infusions for abdominal surgical cases
  - Bolus of 1.5 mg/kg and infusion of 2 mg/kg/hr
- Need for further research
  - With larger study sample sizes
  - Various studies comparing different bolus doses and continuous infusion doses
  - Doses based on TBW, IBW or ABW

Conclusion
- Pain is complex
- Pain is a component of almost all surgical procedures
- Lidocaine infusions are safe, valuable, and inexpensive
- Lidocaine infusions have been shown to decrease post-op pain and decrease the use of opioids in the post-op period
- Improving methods to treat pain increases patient satisfaction

References

References