Volume 7
Issue 1
March 2023
ISSN: 5101195-3

KOSOVA JOURNAL OF SURGERY

PAPERS PRESENTED AT THE SECOND CLINICAL CONGRESS OF THE KOSOVA COLLEGE OF SURGEONS, SEPTEMBER 15-18, 2022

KOLEGJI I KIRURGËVE TË KOSOVËS
KOSOVA COLLEGE OF SURGEONS
MMXVIII

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REVIEW

New aspects of an old drug: Postoperative analgesia with systemic Lidocaine

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Presented at the Second Clinical Congress of the Kosova College of Surgeons (September 15-18, 2022)

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Abstract

Postoperative pain still remains untreated. Common pain treatment with opioids is accompanied with adverse effects like nausea and obstipation. On the other hand, epidural catheter placement is an invasive and expensive procedure.

In recent years, attention has been given to systemic lidocaine in treatment of postoperative pain. The benefits of perioperative and postoperative lidocaine infusions include reductions in pain, nausea, ileus duration, opioid requirement, and length of hospital stay. The non-opioid lidocaine is safe, easy to use and less expensive. The analgesic action of intravenous lidocaine is multifactorial, but still unclear. This mechanism is likely not primarily a sodium channel blockade, but also other effects is described.

More controlled clinical studies with the use of systemic lidocaine in different surgical interventions may bring more relevant information about this analgesic approach.

Keywords: systemic lidocaine, postoperative pain, efficacy, safety

Introduction

Postoperative pain still remains untreated and presents the challenge for anesthesiologists and surgeons. Poorly treated postoperative pain can result in organs and systems dysfunction, like cardiovascular,

pulmonary, gastrointestinal and renal system. The untreated postoperative pain may result in the development of chronic pain

Each year, more than 230 million people undergo surgery worldwide; and more than half of them suffer from severe pain after surgery.[1] In 2011, Institute of Medicine in the US, reported that 80% of patients suffered from postoperative pain, and 88% of them had moderate, severe or extreme pain.[1] The International Association for the Study of Pain (IASP) is trying to bring together scientists and clinicians, to share their knowledge and improve global pain management, and each year, they announce new global initiatives against the pain. 2019 was declared "Global Year against Pain in the Most Vulnerable", which means pain treatment in elderly, infants and young children, in individuals with cognitive impairments and pain survivors of torture, while 2017 was global year against pain after surgery (iasp-pain.org).

The first choice is pharmacological treatment of postoperative pain with opioids. Opioid use is accompanied with adverse effects like nausea and obstipation, and respiratory depression, but opioid overdose and opioid-related deaths are also rising.[2] On the other hand, opioid-free analgesia and anesthesia (OFA) has become popular in recent years.[3] There are data supporting the multimodal approach of non-opioids: nonsteroidal anti-inflammatory drugs (NSAIDs), ketamine, magnesium, anti-inflammatory corticosteroids, alpha-2-adrenergic agonists and delta ligands, and intravenous local anesthetics[3] and the reduced incidence of postsurgical pain.

In this article, we are focused on intravenous use of lidocaine for treatment of acute postoperative pain.

Pharmacologic characteristics of lidocaine

Lidocaine [2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide] is the first modern local anesthetic, a prototype of amino amide derivatives. Lidocaine was discovered in 1946 by Löfgren and Lundqvist, and approved for use in humans by the US Food and Drug Administration in 1948 by the trade name Xylocaine.[4] Intravenous lidocaine was first used for postoperative analgesia in 1958.[5]

Intravenously administered lidocaine is initially distributed to highly vascularized organs (heart, brain, lungs, and kidneys) than to less vascularized organs (adipose tissue, skin, muscle). Lidocaine has a high volume of distribution and around 60-80% of its molecules are bound to plasma proteins (α 1-acid glycoprotein).[6]

About 90% of lidocaine is metabolized in the liver by the microsomal enzyme system (cytochrome P450). Its active metabolites are monoethylglycinexylidide (MEGX) and glycinexylidide (GX). Lidocaine and its metabolites are mainly excreted through the kidneys, while less than 10% is excreted unchanged in the urine. The elimination half-life of lidocaine is between 90 and 120 min in most patients, but may be prolonged in patients with hepatic insufficiency or congestive heart failure.[7]

The wellknown pharmacological action of lidocaine is the blockade of sodium gated channels in neural tissues, which results in interruption of neuronal transmission.[8]

The mechanism of the analgesic effect of intravenous lidocaine is still unknown, however multiple mechanisms regarding the site of action have been proposed, such as Na^+ channel blockade, modulation of K^+ and Ca^{2+} channels, blockade of presynaptic dopamine and muscarinic receptors, inhibition of N-methyl-D-aspartate (NMDA) receptors, direct action on the spinal dorsal horn neurons and reduced conduction and excitability of unmyelinated C fibers. It is likely that there is not just one mechanism responsible for lidocaine-mediated antinociception, but a complex synergy of multiple pathways.[9]

Despite the anti-nociceptive and anti-hyperalgesic action lidocaine also exhibits antiinflammatory, antimicrobial and anticancer effects. Lidocaine is cardioprotective, neuroprotective and anticonvulsant.

Dosage of intravenous lidocaine

An international consensus statement[10] recommended a loading dose of lidocaine no more than 1.5 mg/kg, given as an infusion over 10 minutes; followed by continuouslidocaine infusion, with a rate of no more than 1.5 mg/kg/h^{-1} for no longer than 24 hours. All patients must be closely monitored. If the infusion is extended beyond 24h, the rate of lidocaine infusion must be reduced to approximately 50%.

Lidocaine is considered to have a greater margin of safety than other local anesthetics. Central nervous system toxicity occurs when plasma levels reach 5µg/ml. However, continuous infusion of intravenous lidocaine at clinically relevant doses (1–2 mg/kg/h) usually results in plasma concentrations remaining below this threshold.

Many other factors must be considered to prevent systemic toxicity from local anesthetics, such as the use of other local anesthetics at the same time or within the period of action. The use of intravenous lidocaine is contraindicated in patients with heart failure, hepatic and renal impairment, and in combination with some antiarrhythmics (e.g., amiodarone, disopyramide, quinidine, sotalol) and beta blockers.[11]

Clinicians should be aware of the symptoms of toxic effect of excess lidocaine, and interlipids should be present in places where intravenous lidocaine is applied.[12]

Clinical use of intravenous lidocaine and discution

Intravenous lidocaine is currently used in treatment of postoperative surgical pain in almost all types of surgeries. The use of intravenous lidocaine in abdominal surgery is the most studied and perioperative and postoperative pain in these patients are clinically improved. Use of systemic lidocaine decreases the incidence of postoperative nausea and vomiting and early recovery of bowel function. A meta-analysis from Marret and coworkers[13] concluded that intravenous lidocaine administration decreased the duration of ileus, the length of hospital stay, postoperative pain intensity and the incidence of nausea and vomiting.

Barral et al.,[14] in a randomized control trial (RCT), analyzed 60 patients undergoing major abdominal surgery. Thirty of them received systemic lidocaine during the surgery. The results suggest that perioperative infusion of lidocaine decreases the intensity of postoperative pain, reduces postoperative analgesic consumption, without significant adverse effects. The same results were shown after laparoscopic surgery.[15]

In orthopedic patients, the effect of intravenous lidocaine has been studied during surgery in patients with bone fractures and total joint arthroplasty. Forouzaan et al.[16] concluded that the application of intravenous lidocaine, compared to intravenous morphine, was significantly more effective for pain treatment in patients with bone fractures.

A randomized, double-blind, placebo-controlled study by Sun et. al.[17] analyzed the effect of intravenous administration of lidocaine on postoperative pain in patients following total knee arthroplasty. Pain was measured using the numerical pain scale at rest and during movement. They found that patients in the lidocaine group had lower postoperative pain levels, in addition to shorter hospitalization stays. A study by Nallbani et al.[18] analysed 90 patients undergoing elective total joint arthroplasty and limb fracture repair, and reported significantly lower postoperative pain during rest and movement, and lower rate of use of additional analgesics in the lidocaine group. Some studies have also reported the benefits of intravenous lidocaine infusion for perioperative pain in urogenital and cardiothoracic surgery.[19, 20]

Intravenous lidocaine as an element of multimodal analgesic therapy was analyzed in major spinal surgery in children. In a double-blind RCT study, 41 children who received lidocaine had improved analgesic measures in first 24 hours, and decreased opioid consumption.[21]

In our practice, we have started using intravenous lidocaine for pain treatment in perioperative and postoperative periods of different surgical interventions with a particular focus on neurosurgery and spinal surgery, pediatric surgery and chronic cancer pain patients.

Conclusion

The growing use of intravenous lidocaine presents a revolution in postoperative pain treatment. Systemic lidocaine should be seen as an additional option of analgesia for anesthesiologists. Its administration is lower in cost compared to other medications, and also more achievable and clinically safe. Intravenous lidocaine is a good alternative for efficient analgesia in patients who have any contraindication to neuraxial anesthesia. Further controlled clinical studies examining the efficacy of systemic lidocaine in different surgical interventions would bring more relevant information and promote wider application of this analgesic approach.

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