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Intravenous lidocaine's function in preventing persistent post-operative pain

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ABSTRACT

Background and Goal of Study
Chronic post-operative pain (CPOP) is an increasing public health issue considering its impact on the patients quality of life and and the associated costs for the healthcare system. The incidence of CPOP can be as high as 75%, depending on the surgical procedure and other factors. Lidocaine is a local anesthetic with anti-inflammatory, analgesic and antihyperalgesic properties. Several studies have shown its use in controlling acute post-operative pain when used intravenously. The goal of this study was to define the role of intravenous lidocaine in preventing CPOP.

Materials and Methods
The PubMed database was searched from 2006 and 2019 with the keywords: "*Chronic post-operative pain*" or "*Chronic post-surgical pain*" or "*Chronic pain*" and "*Intravenous lidocaine*". Adequate papers for the purpose of this study were selected.

Results and Discussion
Three randomized controlled trials that met criteria were obtained: two on breast surgery and the other on open nephrectomy. All trials used intravenous lidocaine during surgery, suspending the infusion up to the first 24-hours of the post-operative period. All three of them showed a significant decrease on the incidence of CPOP. There was a 20-fold decrease six months after breast surgery.

Conclusion
Intravenous lidocaine seems to decrease the incidence of CPOP however, there is limited evidence. More trials are necessary to define the efficacy and safety of intravenous lidocaine. A generally accepted definition of CPOP is needed.

Keywords
Chronic pain; Chronic post-operative pain; Chronic post-surgical pain; Intravenous lidocaine.

INTRODUCTION

There is no standardized definition of chronic post-operative pain (CPOP) but it is usually described as persistent pain 2 or more months after a surgical procedure, not explainable by any other cause.[1]

The incidence of CPOP can be as high as 75%, depending on the surgical procedure and other factors, which makes it an increasing public health issue considering its impact on patients quality of life and its associated costs for the healthcare system.[2-5] CPOP is a dysfunction of the nociceptive system and the mechanisms that lead to its development are multifactorial and often poorly understood. The wind-up phenomenon seems to be fundamental to the development of central sensitization and chronic pain. Stimulation of C fibers leads to the synaptic release of glutamate that activates α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors, allowing sodium to leak in the cell and thus propagating the action potential. The intense stimulation of C fibers, for instance after surgery, will result in greater post-synaptic depolarization, which can remove the magnesium ion that normally blocks N-methyl-d-aspartate (NMDA) receptors. Then these also can be activated by glutamate, allowing calcium ions to enter the post-synaptic neuron, increasing the likelihood for this cell to reach threshold for firing an action. This increased status of susceptibility for neuron membrane depolarization is called central sensitization.[2,6,7]

Several risk factors for the development of CPOP are known. These can be divided into two groups of factors: the ones related to the patient, such as young age, female gender or catastrophization of pain; and those associated with surgery (higher invasive techniques with higher pain scores expected or longer surgery duration). Among the most important risk factors for the development of CPOP is acute post-operative pain. Both thehigher the intensity of pain and the longer the post-operative pain remains uncontrolled, the more predictive is chronification of pain. Therefore, the better the analgesic control in the immediate post-operative period, the lower the incidence of CPOP.[2]

The principal mechanism of action of lidocaine [2-(diethyllamino)-N-(2,6 dimethylphenyl) acetamide] as a local anaesthetic is through blockade of voltage-gated sodium channels, inhibiting the propagation of the action potential. This way, lidocaine prevents the conduction of the stimulus by C and Aδ fibers after tissue damage.[8-10] Several other actions has been associated with this drug, such as the blockade of the NMDA receptors (through inhibition of protein kinase C) and the inhibition of the release of anti-inflammatory cytokines such as thromboxane A2 and neurocinines. This intrinsic multimodal set of action (analgesic, anti-inflammatory and antihyperalgesic properties) aroused interest for its use intravenously in the peri-operative period, mainly focusing on acute post-operative pain.[8,11]

The use of systemic lidocaine have been historically limited by safety concerns. This drug is known to cause central nervous system (CNS) and cardiovascular side effects. This usually occur in a predictive manner developing from mild symptoms as circumoral numbness, tongue paresthesia, dizziness, blurred vision and may progress to agitation, muscle twitches, seizures and even CNS depression (unconsciousness and coma). Major cardiovascular toxicity, expressed as severe hypotension and bradycardia or even as life-threatening arrhythmias (ventricular tachycardia and fibrillation) usually presents later, as it needs higher plasmatic lidocaine concentrations to develop. The peri-operative period raises these concerns as the concomitant techniques used for anesthesia may blunt early clinical signs of lidocaine toxicity.

However, several studies shows that therapeutic plasmatic concentrations of intravenous lidocaine seem to be between 1-5 μg/L. Only minor side-effects such as vertigo, somnolence and perioral paresthesia can develop in these plasmatic concentrations. Classic protocols used for intravenous lidocaine in the peri-operative setting are 1.5 to 3 mg/kg bolus followed by 1.5 to 3 mg/kg/h infusion, which had been shown to reach safe therapeutic plasmatic concentrations. Higher concentrations are needed to occur CNS or cardiovascular toxicity.[9,10]

The utility of intravenous lidocaine in reducing the acute pain and opioid consumption in the early post-operative period is well-documented, mainly in abdominal and thoracic surgery. The efficacy of this drug on more painful surgical procedures may be due to its increased affinity for sodium channels when they are opened rather than deactivated (the so called use-dependent or frequency-dependent blockade).[9-11]

Its multimodal properties aligned with its efficacy on more painful surgeries with higher risk of chronic pain, makes intravenous lidocaine a promising technique for preventing CPOP. Hence, the goal of this study is to review recent literature regarding the use of peri-operative intravenous lidocaine in preventing CPOP.

MATERIALS AND METHODS

A literature search was conducted on the main biomedical database, the PubMed database, with the keywords: "*Chronic post-operative pain*" or "*Chronic post-surgical pain*" or "*Chronic pain*" and "*Intravenous lidocaine*". No methodological filters were added to retrieve articles by study type. The search was also limited to English and Portuguese language documents published between January 1, 2006 and December 31, 2019.

In the first-level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. Articles were excluded if they assessed the effect of topical lidocaine, lidocaine injections (including nerve blocks, Bier blocks) and oral lidocaine. Articles were also excluded if they evaluated exclusively acute pain, chronic pain not related to surgery or chronic pain treatment.

RESULTS

A total of forty-two citations were obtained in the literature search. Following screening of titles and abstracts, only nine potentially relevant reports were retrieved for full-text review. Of these potentially relevant articles, three publications were included in this report. All were randomized, double-blind, placebo-controlled clinical trials. Table 1 shows and compares those trials regarding sample, type of surgery, intravenous lidocaine protocol used and results in acute and post-operative pain obtained.

DISCUSSION

There are many literature concerning the use of intravenous lidocaine in acute post-operative pain, however, only three randomized controlled trials, enrolling a total of 158 patients, were found that tried to evaluate the effectiveness of lidocaine in the prevention of CPOP. Two of these trials were on breast surgery and the other one on open nephrectomy. All trials used intravenous lidocaine during surgery, suspending the infusion up to the first 24-hours in the post-operative period.

Our research, as shown in the table, demonstrates that the use of peri-operative intravenous lidocaine a reduces the incidence of CPOP. All three studies found a significant decrease on the incidence of CPOP, besides using different dosage and times of infusion.

Every author accessed CPOP differently which limits the comparison between protocols. A broadly accepted definition of this condition is needed.

Table 1. *Comparison of Trials*

Authors	Surgery	Sample (Lidocaine *vs* Control)	Doses	Duration of Lidocaine Infusion	Post-operative Analgesic Regimen	Acute post-operative pain	CPOP
Grigoras et al[12]	Breast surgery	36 (17 *vs* 19)	Bolus: 1,5 mg/Kg Infusion: 1,5 mg/ Kg/h	Up to 1-h after the end of the surgery	- Morphine sulphate by patient PCA, 1 mg maximally every 5-minutes; no basal infusion; -Diclofenac sodium 50 mg PO/PR, 12 hourly PRN; -Paracetamol 1 g PO/PR, 6 hourly PRN; - Tramadol 100 mg IM/POPRN as rescue medication.	No difference between groups	Assessed 3-months after surgery. CPOP defined as pain related to surgery in the last week Incidence: 5-fold decrease
Terkawi et al[13]	Mastectomy	61 (34 *vs* 27)	Bolus: 1,5 mg/Kg Infusion: 2 mg /Kg/h	Up to 2-h after the end of surgery	Not Standardized	Less pain and analgesic drugs consumption in the lidocaine group	Assessed 6-months after surgery. Incidence: 20-fold decrease
Jendoubi et al[14]	Open Nephrectomy	61:-21 Lidocaine group -20 Ketamine group (Bolus: 0.15mg/Kg/ Infusion: 0.1mg/kg/h) -20 Control group	Bolus: 1.5 mg/Kg Infusion: 1 mg/Kg/h	Up to 24-h after the end of surgery	- Morphine sulphate by PCA, 1 mg maximally every 7-min; no basal infusion. -Paracetamol 1 g, 6 hourly PRN -Nefopam 20 mg IV, 8 hourly PRN.	40% reduction in post-operative acute pain in the lidocaine group	Assessed 3-months after surgery using "neuropathic pain questionnaire" Less incidence of CPOP in the lidocaine group

Both breast surgery and open nephretomy are reported to have a high prevalence of CPOP, 20 to 68% and 4 to 27% respectively.[12-14] There are many other surgical techniques associated with CPOP of which no trial were found. In the studies found, systemic lidocaine was better to reduce incidence of CPOP on breast surgery (up to 20-fold less) rather than on open abdominal surgery. The characteristical dose-dependent or frequency-dependent blockade of lidocaine action may explain this difference.

Interestingly, Grigoras et al[12] found that even when lidocaine fails in reducing acute post-operative pain against placebo, it still considerably decreased the incidence of CPOP. This accounts for the importance anti-hyperlagic properties and NMDA receptor blockade as the lidocaine mechanism in preventing CPOP, and not only by controlling acute pain.

Jendoubi et al[14] has a differently designed study in which it compares lidocaine against placebo and also ketamine (a specific NMDA antagonist drug). In this small sampled trial, lidocaine was superior than ketamine in preventing CPOP after open nephretomy.

Concerning safety, Grigoras et al[12] accessed lidocaine plasmatic concentration at the end of the 1-hour infusion their protocol regarded and it still was on therapeutic range and therefore on safe limit. No side effects or safety concerns were documented in any trial.

Optimal protocol and the usefulness of intravenous lidocaine in other high CPOP incidence surgical procedures such as amputation and thoracic surgery remains to be studied.

CONCLUSION

Lidocaine is a local anesthetic with analgesic, anti-inflammatory and anti-hyperalgesic properties.

Intravenous lidocaine during surgery and up to 24-hours in the post-operative period seems to decrease the incidence of CPOP, even when it fails to reduce the acute post-operative pain.

More trials are necessary to define the efficacy and safety of intravenous lidocaine as well as the optimum dose and duration of infusion.

A generally accepted definition of CPOP is needed.

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