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Research Article

The Effect of Intraoperative Intravenous Lidocaine on Chronic Post-Operative Pain Syndrome: Long Term Perspective

Yaroslav Vasilev*, Alexey Karelov, Nadezhda Marova and Syed Ghufran Arshed

Department of Anesthesia and Intensive Care, North-Western State Medical University, Named After I.I. Mechnikov, Saint-Petersburg, Russia

***Corresponding Author:** Yaroslav Vasilev, Department of Anesthesia and Intensive Care, North-Western State Medical University, Named After I.I. Mechnikov, Saint-Petersburg, Russia.

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Abstract

Post-operative chronic pain syndrome is a great concern among surgical patients. It has always been a challenge and a matter of debate among the perioperative physicians to improve the post-operative outcome of surgical patients. Multi model analgesic regimen with local anesthetic used to decrease the acute and chronic post-surgical pain, but rate of success continues to be dismaying low. In this study we examined the beneficial effects of local anesthetic given parenterally.

Lidocaine has different mechanisms of action which can decrease the level of chronic post-operative pain in long term perspective: it affects the neuronal membranes by binding to and inhibiting voltage-gated sodium channels, interacts with G protein coupled receptors, and NMDA receptors. We conducted a study to evaluate the preventive analgesic efficacy of lidocaine after cholecystectomy.

Ninety six patients undergoing elective laparoscopic cholecystectomy under general anesthesia were studied with almost one half of the patients receiving lidocaine bolus of 1,5 mg/kg before induction and then followed by infusion of 2 mg/kg/h throughout surgery, the other half received the same amount of 0.9% sodium chloride infusion. A blind observer assessed the pain according to MPQ 3, 6 and 12 months after the surgery. A modest reduction in the post-operative chronic pain syndrome after 3 months in patients with lidocaine infusion was observed, however this tendency was not seen after 6 and 12 months.

Keywords: *Intravenous Lidocaine; Chronic Post-Operative Pain Syndrome*

Introduction

Effective postoperative pain control is one of the most important tasks in the surgical patients. Inadequate pain control, apart from being inhumane, results in increased morbidity.

Many surgical patients still experience moderate to severe pain immediately after surgery and in long term perspective, despite multi model analgesic regimen, efforts to develop new drugs and techniques for effective postoperative pain control.

Intravenous lidocaine infusion may be used as an adjuvant drug during and after surgery in patients undergoing mastectomy, laparoscopic cholecystectomy, and laparoscopic colon resection; it is associated with a significant postoperative opioid-sparing effect, earlier return of bowel function or shorter hospital stay.

All causes and provocative factors of CPPS (Chronic Postoperative Pain Syndrome) are still unknown, but we are trying to develop measures to reduce the risk of this complication. The purpose of this study was to determine the effect of intraoperative lidocaine infusion initiated before surgical incision and discontinued immediately after skin closure on chronic postoperative pain in patients undergoing laparoscopic cholecystectomy.

The primary outcome of this single center randomized, and placebo-controlled study was to evaluate the impact of IV lidocaine on CPPS.

Materials and Methods

Following approval of the study protocol by the University ethics committee 96 patients were randomized into 2 groups for participation in this study. Written Informed Consent was obtained from all patients after the explanations about study purpose and procedures to each patient according to the University Protocol.

All patients were ASA class II and III, aged 21 years and older and undergoing elective laparoscopic cholecystectomy under general anesthesia.

Patients were excluded if they were pregnant or had a history of chronic pain syndrome, morbid obesity (BMI > 40), allergy to amide local anesthetics, first and second degree heart conduction blocks, renal, or liver dysfunction, substance abuse disorder, current treatment with antiarrhythmic medications.

96 patients who fulfilled the inclusion and exclusion criteria were randomly allocated into 2 groups of equal size to receive either lidocaine infusion (Lidocaine group), or 0.9% sodium chloride infusion (Control group). None of the investigators involved in patient management were aware of the group assignment.

Lidocaine group (n = 42) patients received a loading dose of IV lidocaine 1,5 mg/kg slowly just before induction of anesthesia, then the lidocaine infusion started at a rate of 2 mg/kg/h. Control group (n = 54) patients received an equal volume of 0.9% sodium.

The infusion in both groups was initiated at the time of anesthesia induction, and continued until the end of the surgery.

All subjects were given thiopental sodium 3 to 5 mg/kg and fentanyl 1 - 2 mkg/kg for induction of anesthesia followed by suxamethonium 1.5 - 2.0 mg/kg for intubation and pipecuronium 0.04 - 0.05 mg/kg IV for neuromuscular blockade. Anesthesia was maintained with isoflurane 1.0 - 1.2 MAC (Minimal Alveolar Concentration) and fentanyl 3- 4 mcg/kg/h.

Postoperative NSAID i.e. ketorolac 30 mg and piperidine 20 mg was administered for pain > 4 on pain numeric rating scale until it is less than 4.

Evaluation of pain was performed after 3, 6 and 12 months after surgery with McGill pain questionnaire (MPQ).

The full version of the MPQ was used for the assessment of pain which has been translated into Russian. This tool is made up of 78 descriptors divided in three categories: sensory (word groups 1 - 10, 17 - 19) described in terms of temporal, spatial, pressure, thermal, and other properties ten items), affective qualities (word groups 11 - 15, 20) described in terms of tension, fear, and autonomic properties; and 3) cognitive qualities or evaluative words (word groups 16, 20) that describe the overall appraisal of the pain five items. Two indices were also used to measure pain through the use of the descriptors: the number of words chosen (NWC) and the pain rating index (PRI). The word in each subclass implying the least pain is given a value of 1, the next word is given a value of 2, etc. The values of the words chosen are then added up to obtain a score for each category (R Melzack, 1975).

The Cytel Studio 8.0 and LePAC 2.0.41 were employed for statistical analysis.

Normally distributed data were analyzed using: nonparametric data were analyzed using the Mann-Whitney U test; and for categorical variables Fisher Exact Test were applied as appropriate. $P < 0.05$ was considered significant.

Results

A total of 96 subjects were enrolled, and 18 subjects left the study after 3 month (control group 66; experimental group 30), leaving 82 subjects (control group, 57; experimental group, 25) for 6 month visit.

Both groups were equivalent in relation to demographic variables, surgical time, and length of infusion.

The incidence of chronic postoperative pain after 3 months was significantly lower in the Lidocaine group than in the Control group (10% vs 37.88.3%, Fisher's Exact Test P = 0.0069) with an overall incidence of 29.2%, and after 6 months 18.3% (16% vs 19.3% accordingly, Fisher's Exact Test P = 1.0).

Value of NWC according to a test Mann Whitney in lidocaine group was significantly less than in Control group after 3 months p = 0,0085 p < α (α = 0,05).

For statistic purpose all patients were distributed in three groups: no pain, minimal pain (less than 3 words were chosen) and severe pain (more than 3 words were chosen). Dates were assessed with Fisher's Exact Test.

The results for CPPS assessment at 3 months after the surgery in the 2 groups are summarized in tables 1-4.

	No pain	Minimal pain	Severe pain
Control, patients	8	17	41
Lidocaine, patients*	0	3	27

Fisher's Exact Test: p-value exact 2-sides: p = 0,0126 < 0,05.*

According to a test Mann Whitney p = 0.011.

	No pain	Pain
Lidocaine, patients*	27	3
Control, patients	41	25

δ = φ1 (Lidocaine) - φ2 (Control) = 0,271

Equal tailed Intervals 95% [0.099, 0419]

99% [0.038, 0.463]

99.9% [-0.036, 0.512]

Table 1: *PRI 3 months after surgery.*

	No pain	Minimal pain	Severe pain
Control, patients	18	7	41
Lidocaine, patients	2	1	27

Table 2: *Sensory category 3 months after surgery.*

p-value exact 2-sides: p = 0,0167 < 0,05.*

	No pain	Minimal pain	Severe pain
Control, patients	23	1	41
Lidocaine, patients	3	0	27

Table 3: *Affective category 3 months after surgery.*

p-value exact 2-sides: p = 0,0157 < 0,05.*

	No pain	Minimal pain	Severe pain
Control, patients	25	0	41
Lidocaine, patients	3	0	27

Table 4: *Cognitive (or evaluative) category 3 months after surgery. p-value exact 2-sides: p = 0,006 < 0,05*.*

Date evaluation of PRI NWC (total and in each of 3 categories) 6 months and 12 months after surgery with Fisher's Exact Test and t Mann Whitney test, could not find any difference in groups.

Discussion and Conclusion

Chronic postsurgical pain (CPPS) is defined as an unpleasant sensory and emotional experience that persists for 3 to 6 months after surgery, if all other sources of pain were excluded. The incidence of chronic neuropathic pain 1 year after surgery is between 0.5% and 1.5% [1].

Incidence of chronic postoperative pain depends on type of surgery and can reach 3% - 56% in case of laparoscopic cholecystectomy [2-4].

The pathogenic mechanisms leading to CPPS are multiple and the most relevant causes are gender, psychosocial factors, preoperative pain at the site of surgery or in other body regions, the type of surgical trauma, nerve damage, acute postoperative pain and inflammatory responses, perioperative analgesia, type of disease, recurrence of malignancy, and adjuvant therapy [5].

One of the potential therapeutic targets in prevention of CPPS are N-methyl-D-aspartate (NMDA) receptors, considering their role in the establishment and maintenance of central sensitization in dorsal horn nociceptive neurons [6-9]. Since activation of the NMDA receptors are required for the development of central sensitization, it was hoped that blockade of NMDA receptor activity by drugs could diminish the incidence of CPPS.

Commercially available NMDA-receptor antagonists include ketamine, nitrous oxide, dextromethorphan, amantadine, memantine and lidocaine. In our study we decided to pay attention to lidocaine.

Lidocaine's administration has peripheral and central action, and involves several mechanisms: it has effects over G protein coupled receptors, NMDA receptors and calcium-activated potassium channels, and produces substance P decrease. In minimal concentration, it inhibits primary afferent fibers abnormal activity.

Inflammation is a key driver of increased nociceptive inputs that occur with peripheral sensitization, and also acts to maintain central sensitization via spinal neuroinflammation [10]. It decreases plasmatic concentration of proinflammatory cytokines in postoperative period [11]. Unfortunately, some studies do not demonstrate so optimistic results, de Oliveira found, that intravenous lidocaine 2 mg/kg/h did not reduce pain severity and plasma levels of IL-6 in patients undergoing abdominal hysterectomy [12].

Lidocaine effectively used for early postoperative pain control for years. Clinical studies show that continuous perioperative infusion of lidocaine in small doses can significantly reduce opioids consumption and level of pain. Unfortunately lidocaine shows its effectiveness primarily in case of visceral pain. Ness at al. found that intravenous lidocaine dose-dependently inhibited visceromotor and cardiovascular reflexes and the evoked and spontaneous activity of neurons excited by colorectal distension [13].

Groudine used boluses of lidocaine 1.5 mg/kg with maintenance 2 -3 mg/min during radical prostatectomy. Postoperative pain was diminished significantly and morphine consumption decreased by 50%, effect lasted 2 - 3 days (88). Yardeni., *et al.* successfully used 1.5

mg/kg of lidocaine for induction and 1.5 mg/kg for maintenance in patients with hysterectomies, they found decreased level of postoperative pain in first 8 hours and no difference with control group after 12 and 72 hours after surgery [11].

A recent meta-analysis found statistically significant reduction of early surgical pain severity in the first four postoperative hours measured by the visual analogue scale (0 to 10 cm); mean difference -0.84 cm, 95% confidence interval -1.10 to -0.59 [14].

Grigoras used lidocaine for patients after breast surgery, they received an IV bolus of lidocaine (1.5 mg/kg in 10 min) followed by a continuous IV infusion at 1.5 mg/kg/h. The infusion was stopped 60 minutes after skin closure. The proportion of patients with CPPS was less in the lidocaine group compared with that in the control group [11.8% (2/17) vs. 47.4% (9/19), respectively; P = 0.031]. Responses to the SF-MPQ (Short Form McGill Pain Questionnaire) revealed greater total pain rating index and present pain VAS in the control group compared with those in the lidocaine group (2.1 ± 5.3 vs. 1.2 ± 4.4; P = 0.039 and 14.6 ± 22.5 vs. 2.6 ± 7.5; P = 0.025) [15].

Myoung Hwa Kim., *et al.* treated 126 female patients undergoing mastectomy with lidocaine and, magnesium (2 mg/kg and 20 mg/kg respectively for 15 minutes immediately after induction, followed by infusions of 2 mg/kg/h and 20 mg/kg/h respectively). At postoperative 3 months, Quality of recovery QoR-40 and SF-MPQ sensitive scores were significantly lower in group of lidocaine [16].

Terkawi., *et al.* used lidocaine for prevention of post-mastectomy chronic pain: bolus 1.5 mg/kg at induction, then infusion at 2 mg/kg/hr, up to 2 hours after the end of surgery CPPS was assessed at 6 months after surgery. Overall incidence of CPPS was 30% and 12% [17].

The optimal dosage and duration of systemic lidocaine administration for the reduction of CPPS is still unclear, infusions at 2 mg/kg/h or above appeared effective, whilst lower doses did not [14]. The proposed mechanisms by which lidocaine modifies the pathophysiology that prevents CPPS point out on greater efficacy of prolonged lidocaine exposure, however many operative procedures associated with a high incidence of CPPS performed in fast track manner and this imposes practical limitations on infusion durations. Similar to most studies evaluating IV lidocaine in the perioperative period, we chose a relatively short-time interval for IV lidocaine administration.

The main finding of our study is that perioperative lidocaine infusions appear to reduce the incidence of CPPS when assessed around three, but not six and twelve months after surgery.

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Competing Interests

I declare that I have no significant competing financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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