Multiple lidocaine infusions for relief of neuropathic pain: systematic review and meta-analysis

Participants:
Antonio Silvinato[1]
Idevaldo Floriano[1]
Wanderley Marques Bernardo[2]

Created on: 22 May, 2020

1. Programa Diretrizes da Associacao Medica Brasileira, Sao Paulo, SP, Brasil
2. Coordenador do Programa Diretrizes da Associacao Medica Brasileira, Sao Paulo, SP, Brasil

E-mail: wmbernardo@usp.br

http://dx.doi.org/10.1590/1806-9282.66.5.583

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

INTRODUCTION

Chronic pain can be broadly classified into three categories of causation: due to a tissue disorder or injury (nociceptive); due to a somatosensory disorder or injury (neuropathic pain), or a combination of nociceptive and neuropathic pain (mixed pain). Neuropathic pain due to an injury or disease affecting the somatosensory system [1] continues to be a challenging clinical problem because the pain is often severe and incapacitating [2]. Population studies indicate that its prevalence ranges from 7 to 10%, based on validated screening tools [3].

The effectiveness of certain antidepressants, anticonvulsants, opioid analgesics, and various agents has been established in systematic reviews [4] and several evidence-based guidelines for the management of neuropathic pain [5]. However, these studies consistently show that less than 50% of the patients achieve adequate control of pain in the short term, and a recent prospective study, of observational results, showed that only about a quarter reached clinically significant improvement in pain and function in the long term, after up to 12 months of follow-up [6].

Lidocaine has the ability to block sodium channels. Therefore, it can be expected to act only in the subset of neuropathic symptoms mediated by the abnormal activation of the sodium channels [7].

Intravenous infusions of lidocaine in the dose of 5 mg kg-1 provide significant relief of pain in comparison with a placebo, for up to six hours after the infusion, with a peak of 1 to 2 hours after the infusion [8].

Given the short-term effect of systemic lidocaine and the intravenous route, it would not be practical for the management of pain in the long term. Given this, it is justified to evaluate, in the long term, the role of the intravenous infusions of lidocaine in the treatment of chronic neuropathic pain.

OBJECTIVE

The goal of this assessment is to identify the efficacy and safety of multiple infusions of lidocaine in the relief of pain in patients with neuropathic pain, in comparison with a placebo.

METHODS

The clinical question is: What is the impact of therapy with multiple infusions of lidocaine on outcomes of pain relief for up to four weeks and adverse events in the treatment of patients with neuropathic pain, compared with a placebo?

The eligibility criteria for the studies are:

1. An adult patient with neuropathic pain due to any cause;
2. Treatment with multiple applications of intravenous lidocaine compared with placebo therapy;
3. Outcomes - pain relief for up to four weeks and adverse events;
4. Excluded outcomes - evaluation of relief of pain in the period immediately after the infusion, i.e., soon after the infusion and up to 1-3 days after the infusion;
5. Randomized clinical trial;
6. No time or language restrictions;
7. Full text available for access.

The search for evidence was carried out the virtual databases Medline/Pubmed using the following search strategy - (Intravenous OR infusions OR infusion OR parenteral OR systemic) AND (lidocaine OR lignocaine) AND (Pain OR fibromyalgia OR Neuralgia OR Peripheral Nervous System Diseases OR Neuromuscular Diseases OR Nervous System Diseases OR Neuropathic Pain OR Neuralgia, Postherpetic OR Diabetic Neuropathies OR Peripheral Nerve Injuries) AND Random*; and on CENTRAL / Cochrane with the search strategy - (Intravenous OR infusions OR infusion OR parenteral OR systemic) AND (lidocaine OR lignocaine) AND (neuropathic pain). The search in these databases was performed up to the month of March 2020, and a systematic review was performed according to the PRISMA recommendations. [9]

We extracted the following data from the studies: name of the author and year of publication, study population, intervention and comparison methods, pain scores as mean (SD), the absolute number of adverse events, and time of follow-up.

Randomized clinical trials will have their risk of biases analyzed according to the following criteria: randomization, blinded allocation, double-blinding, losses, prognostic characteristics, presence of relevant outcome, time for the outcome, the method for outcome measurement, sample size calculation, early interruption, presence of other biases.

The results were expressed by the difference of the mean (SD) of the pain scores, or the risk of adverse events between therapy with multiple lidocaine infusions and a placebo treatment. No distinction was made on the severity of each adverse event. The confidence level adopted was 95%.

The results of the studies included will be meta-analyzed by RevMan 5.3[10], and the difference in overall risk or mean will be the final measurements used to support the synthesis of evidence that will answer the clinical question of this review.

The quality of evidence will be graded as high, moderate, low, or very low using the GRADE instrument[11] and taking into account the risk of bias, the presence of inconsistency, vagueness or indirect evidence in the meta-analysis of the outcomes (pain relief and adverse events), and the presence of publication bias.

RESULTS

The search for evidence retrieved 1,031 papers, of which 30 studies on intravenous lidocaine therapy were selected based on their title and abstract, for the treatment of patients with various etiologies of neuropathic pain, in comparison with a placebo. The 30 studies were accessed for analysis of the full text. Of the 30 studies, three (parallel RCTs) were selected, for meeting all the eligibility criteria, to support this assessment[12-14]; the grounds for exclusion and the list of studies excluded are available in the references, *Figure 1*, and *Table 5* in the *ANNEXES*.

The population included is of 110 patients with neuropathic pain who underwent therapy with infused lidocaine over a period of one hour, once a week, for 4 weeks (N=55), compared to a placebo (n =55), and followed-up to measure the outcomes of pain relief and adverse events after 4 weeks (Table 1).

Regarding the risks of bias of the 3 studies included [12-14], 2 of them presented uncertainty in the blinded allocation and two uncertainty in double-blinding. Two did not carry out analysis by intention to treat (Table 2).

All studies assessed the outcome of pain relief for up to four weeks after multiple infusions and adverse events (Table 3). The overall risk of bias among the studies is moderate.

TABLE 1. CHARACTERISTICS OF THE STUDIES INCLUDED

STUDY	Study design	Population	Intervention	Comparison	Evolution time
Vlainich et al. 2010[12]	RCT	30 patients; 44.7 ± 10.5 years in the saline group, and 40.9 ± 11.6 years in the lidocaine group; patients with fibromyalgia Exclusion criteria: changes in thyroid, rheumatic, renal, and hepatic function, trauma, rheumatic, neuromuscular, or psychiatric diseases, infectious arthritis, other pain syndromes.	N = 15; Lidocaine 240 mg diluted in 125 ml of saline, infused over a period of 1 hour, once a week, for 4 weeks. All patients received amitriptyline.	N = 15; 0.9% saline All patients received amitriptyline	4 weeks
Albertoni et al. 2016[13]	RCT	42 patients; 47 ± 9.8 years in the saline group, and 42.4 ± 9.4 years in the lidocaine group; patients with fibromyalgia. Patients were excluded if: abnormal laboratory tests; trauma; known psychiatric, rheumatic, neuromuscular or liver diseases; arrhythmia; heart failure, recent myocardial infarction, glaucoma, hypothyroidism or hyperthyroidism; infectious arthritis; another painful syndrome.	N = 19 Lidocaine 240 mg diluted in 125 ml of saline infused over a period of 1 hour, once a week, for 4 weeks. All patients received amitriptyline	N = 19 0.9% saline All patients received amitriptyline	4 and 8 weeks
Kim et al. 2018[14]	RCT	43 patients; 62.71 ± 13.06 years in the saline group, and 62.86 ± 12.5 years in the lidocaine group; patients with postherpetic neuralgia (PHN), and complex regional pain syndrome (CRPS) type II; NRS pain greater than or equal to 4 for at least 3 months, without satisfactory pain relief, with the conservative treatment Patients were excluded if: fibromyalgia, diabetic polyneuropathy, medullary injury; concomitant severe systemic diseases such as myasthenia gravis, decreased pulmonary function, liver problems, severe renal insufficiency, shock or hypokalemia or hyperkalemia, cardiac arrhythmia; psychiatric disorders (schizophrenia, somatization or acute anxiety).	N = 21 Lidocaine 3 mg/kg infused over a period of 1 hour, once a week, for 4 weeks. No changes in analgesics were allowed, including non-steroidal anti-inflammatory drugs, opioids, anticonvulsants, and antidepressants, with the exception of acetaminophen as a rescue analgesic drug.	N = 21 0.9% saline	4 weeks

RCT = Randomized Clinical Trial; NRS = 11-point numerical rating scale; N = number of patients.

TABLE 2. NEUROPATHIC PAIN THERAPY WITH MULTIPLE LIDOCAINE INFUSIONS. DESCRIPTION OF THE RISK BIASES OF THE STUDIES INCLUDED

Study	Random	Allocation Blinded	Double Blind	Losses	Characteristics (prognostic)	Outcomes	Sample calculation	ITT	Early termination
Vlainich 2010[12]									
Albertoni 2016[13]									
Kim 2018[14]									

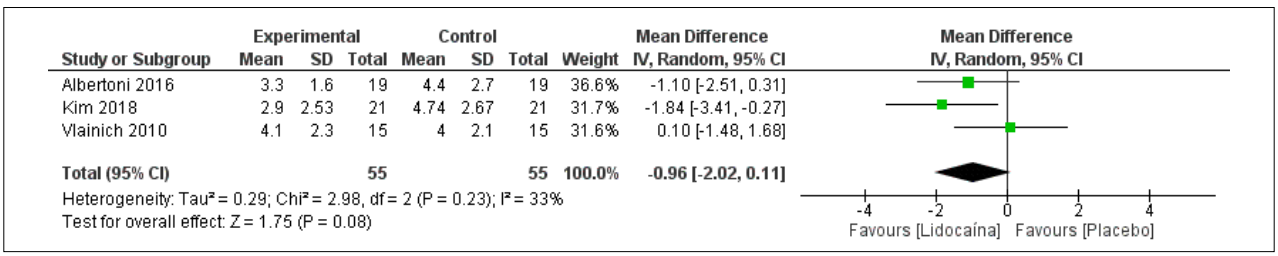
Description of the biases of the studies included (orange = presence; blue = absence; Yellow = unclear risk of bias) ITT = analysis by intention to treat

The three studies allowed the assessment of the outcome of neuropathic pain relief for up to 4 weeks, comparing infused lidocaine once a week, for 4 weeks, with a placebo (saline solution 0.9%); there was no difference in pain reduction between the two groups (MD -0.96; 95% CI -2.02 to 0.11; p = 0.08, I^2 = 33%), Figure 2.

TABLE 3. STUDY RESULTS FOR THE OUTCOME OF DEATH.

Study	Pain scale used	Lidocaine Mean (SD)	Placebo Mean (SD)
Vlainich 2010[12]	VAS 10	4.1 (2.3)	4 (2.1)
Albertoni 2016[13]	VAS10	3.2 (1.6)	4.4 (2.7)
Kim 2018[14]	VAS 10	2.9 (2.53)	4.74 (2.67)

FIGURE 2. COMPARISON FOREST PLOT: 1 LIDOCAINE VERSUS PLACEBO, OUTCOME: 1.1 PAIN RELIEF AFTER 4 INFUSIONS (ONCE A WEEK) OF LIDOCAINE.



ADVERSE EVENTS

The three parallel RCTs included in this review do not allow to assess the safety of IV lidocaine due to a lack of data; therefore, the result of a systematic review with meta-analysis[15], which included crossover studies that evaluated the relief of neuropathic pain (various etiologies) soon after the infusion and up to 1-3 days after the infusion will be used to answer the clinical question. Dizziness, drowsiness, perioral paresthesia, nausea, headache, dysarthria, dry mouth, metallic taste were some of the most common side effects observed in the studies included in this meta-analysis. Three hundred and seventeen patients received lidocaine, while 318 received a placebo. One hundred and thirty-two patients (41.6%) in the lidocaine group experienced adverse events, in comparison with 53 patients (16.7%) in the placebo group (increase in the absolute risk of 25%, 95% CI 18.1 to 31.7%; NNH = 4, 95% CI 3 to 6).

QUALITY OF EVIDENCE: OUTCOME OF PAIN RELIEF IN 4 WEEKS

Summary of Results: Lidocaine in multiple infusions compared to a Placebo for neuropathic pain

Patient or population: neuropathic pain
Background: Therapeutic efficacy and safety
Intervention: Lidocaine in multiple infusions
Comparison: Placebo

Outcome Nº of participants (studies)	Relative Effect (95% CI)	Potential absolute effects (95% CI)			Certainty	Comments
				Difference		
Pain relief after 4 lidocaine infusions (once a week) Follow-up: 4 weeks average No. of participants: 110 (3 RCTs)	-	The average pain relief after 4 infusions (once a week) of lidocaine was 0	-	MD 0.96 lower (2.02 lower for 0.11 higher)	⊕⊕⊕○ MODERATE	None
Adverse events with the use of intravenous lidocaine Nº of participants: 635 (15 RCTs)	RR 2.50 (1.89 to 3.30)	16.7%	41.6% (31.5 to 55)	25.0% more (18.1 more to 31.7 more)	⊕⊕○○ LOW [b]	None

* The risk in the intervention group (and its confidence interval of 95%) is based on the risk assumed in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; MD: Mean difference; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

SYNTHESIS OF EVIDENCE

In patients with neuropathic pain, infused lidocaine once a week, for 4 weeks, compared with a placebo (saline solution 0.9%) showed no difference in pain reduction in up to 4 weeks. Moderate quality of evidence.

Intravenous lidocaine increases the risk of adverse events (any) in 25% (95% CI 18 to 31%) in comparison with a placebo (saline solution 0.9%), and it is necessary to treat 4 patients for one to present an adverse event (95% CI 3 to 6). Low quality of evidence.

Dizziness, drowsiness, perioral paresthesia, nausea, headache, dysarthria, dry mouth, metallic taste are some of the most common side effects.

DISCUSSION

A large number of trials tested IV lidocaine for neuropathic pain; however, most included few patients (<30) and reported the use of a diverse range of dosages and times of infusion. These studies also assessed pain scored after several periods of time, and most evaluated the efficacy of IV lidocaine in the period immediately post-infusion and in a single dose, while only 4 assessed lidocaine transfused over a period of 4 weeks, to study its persistent effect in the long term.

Our assessment suggests that the effect of lidocaine in humans is transitory and does not last for a long period of time, which can be explained by the pharmacokinetics of the drug. It starts acting between 30 and 60 min and its effects can last from 2 to 6 hours after the end of the infusion, after which the analgesic effect disappears quickly [8].

Based on the retrieved results, we have shown that patients receiving IV lidocaine are more prone to adverse events in comparison with placebo; however, no serious adverse event was reported.

It was not possible to perform a subgroup analysis based on the specific etiology of neuropathic pain, considering the limited number of studies available.

ANNEXES

The selection of retrieved from the virtual databases of scientific information is detailed in the flowchart below:

FIGURE 1. FLOWCHART

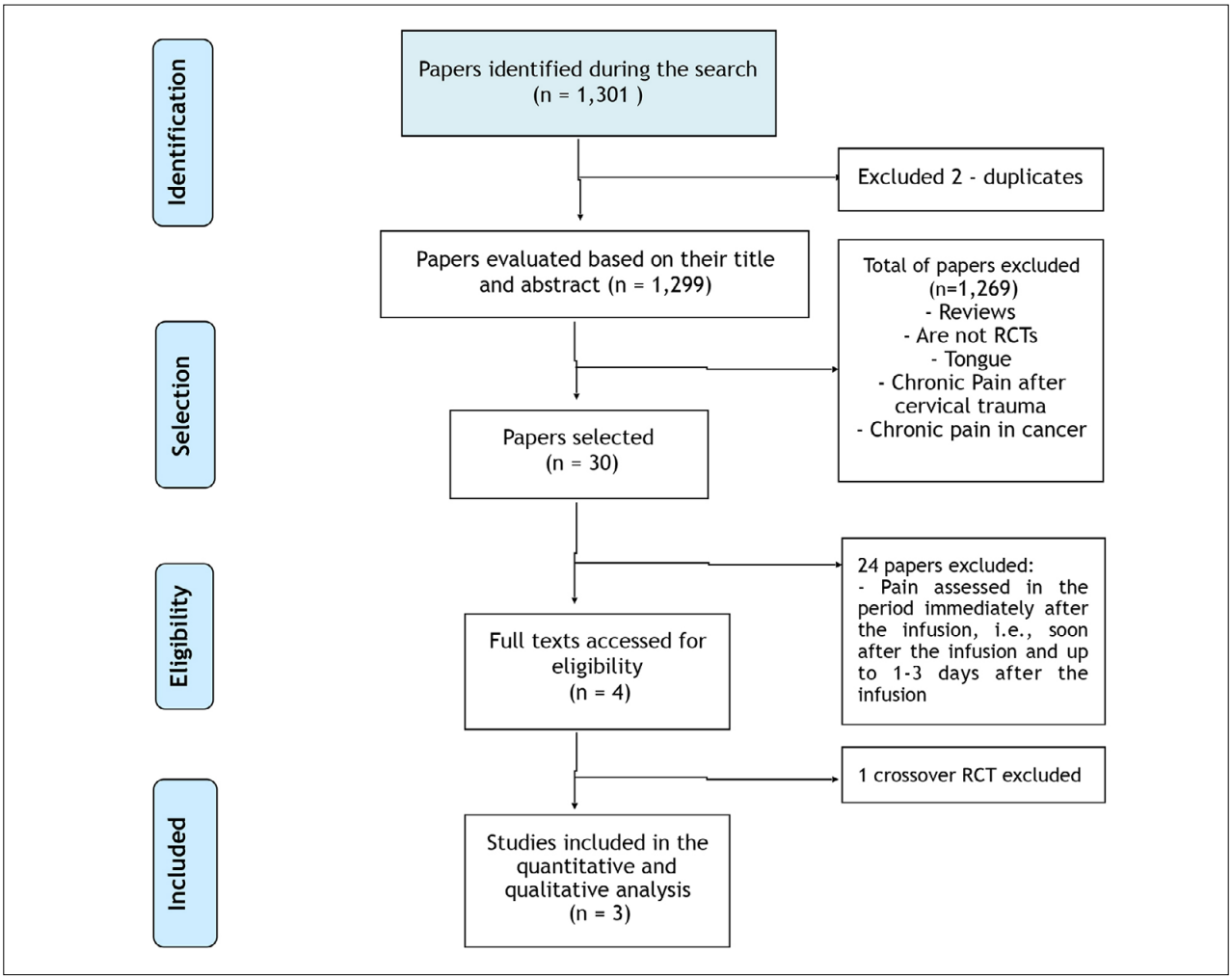


TABLE 4. PAPERS EXCLUDED AND REASON FOR EXCLUSION AFTER READING THE FULL TEXT

Study	Reason for exclusion
Moulin DE, et al. 2019	Crossover RCT without data from the first phase

REFERENCES

1. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008; 70: 1630-5.
2. Gilron R, Watson CPN, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. CMAJ 2006; 175: 265-75.
3. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain 2006; 7: 281-9.
4. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 2012; 85: S3-14.
5. Attal N, Cruccu G, Baron R, et al. European Federation of Neurological Societies. EFNS Guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010; 17: 1113-23.
6. Moulin DE, Clark AJ, Gordon MD, et al. Long term outcome of the management of chronic neuropathic pain – a prospective observational study. J Pain 2015; 16: 852-61.
7. Attal N, Rouaud J, Brasseur M, Chauvin M, Bouhassira D. Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. Neurology. 2004;62:218–225.
8. Challapalli V, Tremont-Lukats IW, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane Database Syst Rev 2005; 19: CD003345.

9. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Disponível em: www.prisma-statement.org.

10. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

11. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.

12. Vlainich R, Issy AM, Sakata RK. Effect of intravenous lidocaine associated with amitriptyline on pain relief and plasma serotonin, norepinephrine, and dopamine concentrations in fibromyalgia. Clin J Pain 2011;27:285-8. PMID: 21178598

13. Albertoni Giraldes AL, Salomão R, Leal PD, Brunialti MK, Sakata RK. Effect of intravenous lidocaine combined with amitriptyline on pain intensity, clinical manifestations and the concentrations of IL-1, IL-6 and IL-8 in patients with fibromyalgia: A randomized double-blind study. Int J Rheum Dis. 2016;19:946-953. PMID: 27309886

14. Kim YC, Castañeda AM, Lee CS, Jin HS, Park KS, Moon JY. Efficacy and Safety of Lidocaine Infusion Treatment for Neuropathic Pain: A Randomized, Double-Blind, and Placebo-Controlled Study. Reg Anesth Pain Med 2018;43:415-424. PMID: 29381569

15. Zhu B, Zhou X, Zhou Q, Wang H, Wang S, Luo K. Intra-Venous Lidocaine to Relieve Neuropathic Pain: A Systematic Review and Meta-Analysis. Front Neurol 2019 18;10:954. PMID: 31620064