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Are Lidocaine Infusions the Future of Chronic Pain?

Clara Gilbert

Hayley Loos

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Clinical Scenario

Michelle is a 45 year-old woman who presents to her primary care provider with non-specific lumbar pain. The pain has been present for three years and previously has been managed with oxycodone. Michelle's provider knows the risks of opioid misuse and would like to offer her another therapy to reduce and possibly discontinue the oxycodone. After doing research into adult patients with non-cancer chronic pain for treatments that can improve pain, the provider's question is: among non-cancer adult chronic pain patients, do IV lidocaine infusions compared to placebo decrease pain after at least one month of use?

Abstract

Background: Chronic pain is a global issue that can affect anyone at any stage of life. Researchers have spent decades developing innovative solutions for pain relief, especially in response to the current opioid epidemic. One up-and-coming solution is that of intravenous (IV) lidocaine infusions for adult non-cancer chronic pain patients and the extent of pain reduction following treatment.

Method: This literature review was conducted through PubMed using the terms "intravenous lidocaine" and "chronic pain". Articles were excluded if there were post-surgical and cancer pain patients. Three studies were included in the subsequent qualitative synthesis. One study was an RCT and the other two were retrospective chart reviews.

Results: Moulin et al. showed no statistically significant impact on the intensity and duration of patient pain when compared with the control group that was given a placebo infusion. In contrast, Iacob et al. and Wilderman et al. showed that the IV lidocaine infusion did improve pain for a portion of the patients, some of whom elected to continue the infusions due to the beneficial effects.

Conclusion: Lidocaine infusions have very little risk of side effects, which leads to the discussion of the risks versus the benefits of potential pain relief without exposure to chronic opioid use and eventual misuse. This literature review showed that there is very little research done on the potential benefits of IV lidocaine infusions in treating non-cancer chronic pain.

Introduction

Chronic pain does not discriminate. At least 20-35% of the world population has personal experience with chronic pain.[1] By definition, non-cancer chronic pain lasts at least 3 months and is not related to malignancy.[2] The prevalence of this pain and the implications it has on patient's lives has made it a target for researchers and pharmaceutical companies for decades. In the 1990s, opioid prescriptions for pain management were encouraged by policies and professional societies, without much concern for the future ramifications.[3] The level of dependency and addiction from opioids led to a climax in 2016, when researchers and public officials declared an "opioid epidemic". The reaction of the healthcare community has been strong and swift, with many providers refusing to prescribe opioid medications altogether. Unfortunately, this response has left chronic pain patients without a viable alternative for pain management.

IV lidocaine is a promising alternative to opioids for the treatment of chronic non-cancer pain. Lidocaine is a commonly used topical anesthetic, local anesthetic, and antiarrhythmic.[4] Lidocaine reduces pain by blocking sodium channels and subsequently preventing nerve depolarization.[4] Lidocaine exerts anti-inflammatory effects by decreasing the expression of pro-inflammatory cytokines and other immunological mediators.[5] The combination of the two mechanisms of action makes lidocaine a useful agent for non-cancer pain management. The anti-inflammatory effects of lidocaine promote pain reduction long after peak plasma concentrations are reached, which is within 30-120 minutes following administration.[5] The extent of long-term pain reduction is thus far poorly understood. This review will focus on recently published evidence investigating the utilization of a singular IV lidocaine infusion as an adjunctive treatment for adult non-cancer chronic pain patients and the extent of pain reduction at two or more weeks post-administration.

Methods

An initial search of PubMed was performed in September of 2022 using the terms "intravenous lidocaine" and "chronic pain" and resulted in 56 articles with duplicates removed. Articles were removed if they were published more than 10 years ago. These parameters resulted in the exclusion of 14 articles. The 28 remaining articles were assessed for eligibility. Articles were excluded due involvement with post-surgical and cancer pain patients. The final three studies were included in qualitative synthesis.

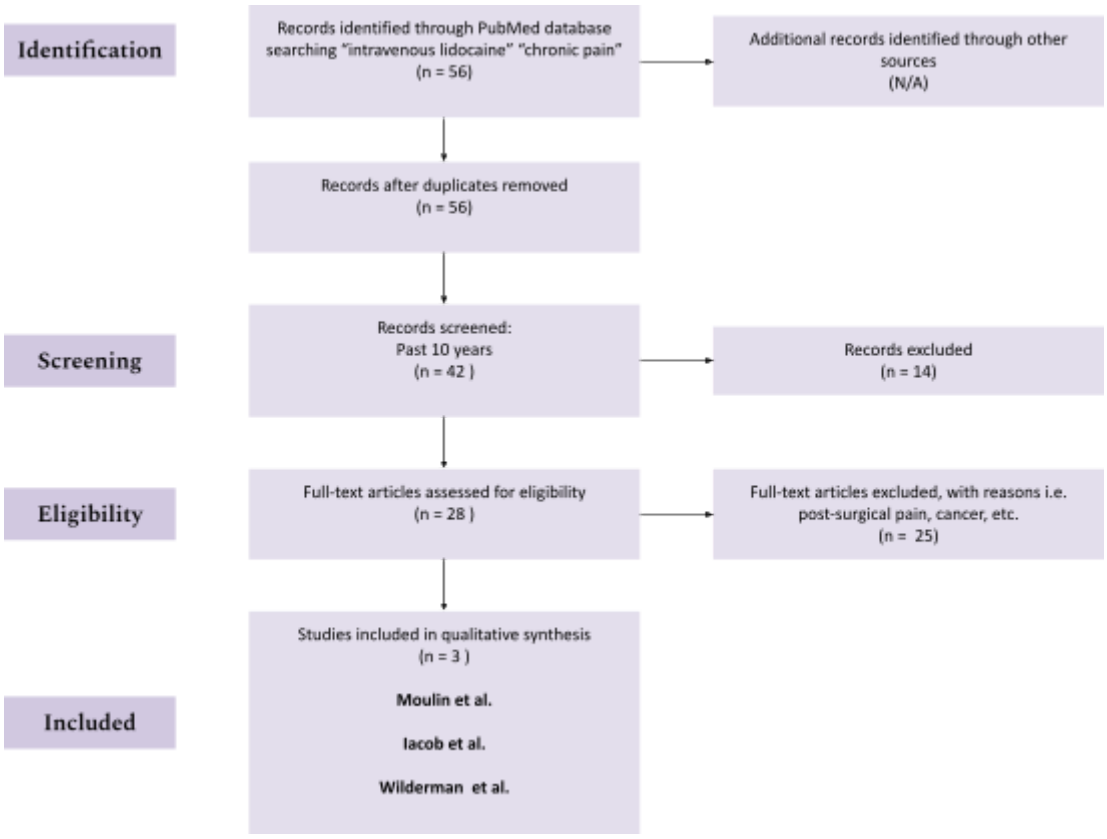

Chart 1: PRISMA flow sheet for selection of eligible literature review articles.

Results

Study #1 (Moulin et al.)

Intravenous lidocaine in the management of chronic peripheral neuropathic pain: a randomized control trial

Objective

An RCT to determine if lidocaine provides significant neuropathic pain relief after four weeks post-infusion when compared to placebo.

Study Design

The study was a single site, randomized, double-blind, crossover trial completed at a neuropathic pain clinic in London, Ontario. Participants were recruited from this center between September 2011 and August 2015 as well as through an advertisement in the local paper. The participants were triaged by the research nurse and then selected by the principal

investigator after a full medical assessment. The participants were chosen based on specific exclusion and inclusion criteria (Table 1). A total of 324 participants were screened and 105 were deemed eligible. Of the eligible participants, 71 were excluded due to transportation barriers and undisclosed reasons. The remaining 34 patients were randomly divided into experimental and control groups.

The intervention involved 1:1 allocation ratio of either IV lidocaine or diphenhydramine, the placebo. The pharmacy concealed the infusions from the administering nurse and principal investigator. The lidocaine was given at 5 mg/kg in 250 of normal saline while the placebo was given as 50 mg of diphenhydramine in 250 of normal saline. The patients were monitored through continuous cardiac monitoring, oximetry, and blood pressure every 5 minutes during the duration of the infusion and for 30 minutes after. The patients continued to take their prescribed medications and over-the-counter analgesics. The patients recorded their pain scores in a diary and spoke with a research nurse weekly. Pain scores were recorded at baseline, six hours, and daily for four weeks. Additionally, secondary outcomes were measured. These included the Pain Interference Scale of the Brief Pain Inventory for Physical Function, LEEDS Sleep Evaluation, Hospital Anxiety and Depression scale for Mood, Patient Global Impression of Change for Global Satisfaction, and EQ-5D health outcome. The values for these measures were obtained at baseline, days 1, 3, 7, 14, 21, and 28. Data about patient demographics and baseline analgesics was collected. At six weeks, the patients were crossed over to the other infusion.

Inclusion Criteria	**Exclusion Criteria**
18-80 years of age	Clinically significant cardiac disease (unstable angina, congestive heart failure, or arrhythmias)
Chronic neuropathic pain of peripheral origin present for at least six months	Poorly controlled seizure disorder
Average pain intensity of ≥5 on the 0-10 pain scale over three days	Cognitive or language barriers
Score of ≥4 on the DN4 questionnaire	Allergic history to amide local anesthetic infusions
	Prior treatment with a local anesthetic infusion
	Recreational drug use within the last two years

	Neuropathic pain due to cancer, complex regional pain syndrome, fibromyalgia, neck pain, or back pain

Table 1: Participant Inclusion and Exclusion Criteria for Study 1.

Study Results

At the completion of the four weeks, the average difference in pain scores between lidocaine and placebo were not significant (RR 0.17, 95% CI 0.50 to 0.84, p=0.61) (Table 2). There was no difference in pain scores at any time points during administration and after. The differences between the secondary outcomes were also not statistically significant (Table 2). Side effects between the lidocaine and placebo infusion were similar. The average age of a participant was 58 (12), length of pain duration was 89 (57) months, and average pain intensity was 6.5 (1.2).

	Baseline		Week 4 post-infusion			
	Placebo group	Lidocaine group	Placebo infusion	Lidocaine infusion	Between-group difference (95% CI)	*P* value
Average pain intensity BPI*	6.4 (1.5)	6.5 (1.6)	6.6 (2.0)	6.8 (1.6)	0.7 (− 0.50 to 0.84)	0.61
Pain interference score BPI	6.7 (2.3)	6.5 (2.6)	6.2 (2.7)	6.1 (2.6)	0.03 (− 0.79 to 0.85)	0.94
HADS anxiety depression	9.3 (4.7)	9.4 (4.4)	8.7 (5.7)	9.4 (5.2)	0.60 (− 0.77 to 1.97)	0.38
	10.8 (4.9)	10.2 (5.2)	11.1 (5.7)	10.8 (5.2)	0.05 (− 1.59 to 1.69)	0.95
EQ-5D	0.5 (0.2)	0.6 (0.2)	0.5 (0.2)	0.5 (0.2)	− 0.0 (− 0.11 to 0.05)	0.46
PGIC	3.3 (0.7)	3.2 (0.8)	3.3 (0.9)	3.3 (0.9)	0.12 (− 0.26 to 0.51)	0.51
LEEDS	27.4 (13.1)	29.8 (14.0)	30.2 (13.5)	28.1 (12.6)	− 0.6 (− 2.4 to 1.1)	0.46

BPI = Brief Pain Inventory (0–10); CI = confidence interval; EQ-5D = Quality of Life Health Outcome Instrument; HADS = Hospital Anxiety and Depression Scale (0–42); LEEDS = Sleep Evaluation Questionnaire (0–100; lower score indicates lower quality sleep); PGIC = patient global impression of change (0–10). Mean (standard deviation)

* Mean of daily average pain scores for week 4

Table 2: Primary and Secondary Outcome Measurements for Study 1.

Study Critique

The strength of the study was high because the study was a single site, randomized, double-blind, crossover trial. However, there are numerous weaknesses that limit usefulness of the outcomes. The study only included 34 patients by the completion of the 12 weeks. Additionally, the study was conducted on patients with longer durations of pain with the average being seven years. The types of neuropathies present in the participants were limited because 80% had diabetic neuropathy. It is possible that other causes of neuropathic pain such as entrapment neuropathies and central neuropathic pain syndromes could have a better response to the lidocaine infusions. The author stated that measuring serum levels of lidocaine

may be an important factor in its use with chronic pain. Sudden pain relief may occur within a narrow therapeutic index as stated by the authors. Since the dose was based on mean total body weight then it is possible that some participants did not reach a high enough concentration to achieve reduced pain scores on the day of administration.

Study #2 (Iacob et al.)

Tertiary Care Clinical Experience with Intravenous Lidocaine Infusions for the Treatment of Chronic Pain

Objective

To investigate the extent of long-term chronic pain relief from intravenous lidocaine infusions offered at a pain management clinic.

Study Design

This study was a retrospective chart review study completed at the University of Utah between July 2015 and July 2021. The participants were selected from a pool of patients who were treated at the University of Utah Pain Management Center (PMC). The patients were selected based on if they received their first IV lidocaine infusion at this tertiary pain center. Once the patients were identified in the system, the search extended to include data about their initial new patient visit and following office visits. The information was collected from EPIC EMR with a total of 233 patients and 469 visits analyzed for IV lidocaine infusions by the two principal investigators. A subset of 261 records from the pool were reviewed by PMC physicians to ensure inter-rater reliability. Data collected included demographics, pain assessment variables, location of infusion, diagnoses, side effects, and pre/post pain scores.

The study focused on pain relief during and following IV lidocaine infusions. The focus of the data collected was about the amount of pain relief and duration. The researchers characterized relief of less than four days as no prolonged benefit. Relief with a duration of four to six days was coded as “unclear prolonged benefit”. Documentation of pain location was classified by body region then subtype into types of neuropathic pain (ex. chronic regional pain syndrome, and trigeminal neuralgia). Non-neuropathic categories of pain included migraines/headaches, posttraumatic, and postsurgical.

IV Lidocaine infusions were administered using the PMC protocol of 1,000 mg/h for up to 30 minutes. The patients were monitored by a PMC nurse for vital signs, pain levels, and side effects. The infusion was halted if patients reported side effects such as nausea, dizziness, or vomiting. A nurse contacted the patients 24 to 72 hours following infusion to collect information about treatment benefits, side effects, and other concerns. Four week follow-up visits were scheduled based on the patients' discretion. Some patients underwent second and third subsequent lidocaine infusions.

Study Results

The researchers in this study focused on pain reduction and duration of benefit while analyzing patient demographics, treatment doses, and side effects. The average pain score before the first infusion was 5.67 (SE=0.10) and 2.38 (SE=0.11) following administration ($p<0.001$). Of the 233 patients, 41% were defined as having benefitted, which means they reported pain reduction seven days after infusion. Inversely, 40% reported no benefit. The percent of patients who were classified as having benefited increased for the second and third infusions. Patients that reported pain reduction from the first infusion were more likely to follow-up for the second infusion when compared to those who did not benefit (92% vs 36%, $p<0.001$). This trend continued for the third infusion. Only 98 of the 233 patients' charts provided information about duration of benefit for the IV lidocaine infusions. Following the first infusion, 40% of patients were characterized as having no long-term benefit (less than seven days), 40% had benefits for one to two weeks, 16% for two to three weeks, and 8% for three or more.

The study highlighted demographic information, treatment doses, and side effects as adjuvant data to the pain reduction results. The average age of the patients was 51 (SD=15.0 years), 54% were female, and the average pain duration was 7.7 years (SD=9.5 years). A majority of the patients were diagnosed with neuropathic pain. The first infusion was classified as a challenge dose. The average dose administered was 381.4 mg (SD = 120.9 mg) over an average of 23 minutes (SD = 7.24 minutes). Common side effects included peripheral numbness, dizziness, tinnitus, and perioral numbness.

The authors concluded that 41% patients reported clinically meaningful extended pain relief after their first treatment and 94% returned to the clinic for a second infusion of IV lidocaine. A majority of the patients in the study had neuropathic pain. A significant subset of

patients with non-neuropathic pain reported beneficial pain reduction supporting the use of IV lidocaine for other chronic pain patients.

Study Critique

This study is currently the largest retrospective study on the long-term benefit of IV lidocaine infusions for patients with chronic pain. However, the study lacked strength because it was a retrospective chart review rather than an RCT. The charts were incomplete and missing important data, which could alter final conclusions. Additionally, the patients in this study remained on their prescribed medications, which makes it difficult for patients to discern pain relief from lidocaine or from their other medications. Future studies should document this more thoroughly as well as completing more detailed assessments of pain relief, changes in pain severity, and more specific duration of pain relief. The authors also stated that studies should focus on placebo-controlled frameworks to limit the effects of placebo response on outcomes.

Study #3 (Wilderman et al.)

Repeated Intravenous Lidocaine Infusions for Patients with Fibromyalgia: Higher Doses of Lidocaine Have a Stronger and Longer-Lasting Effect on Pain Reduction

Objective

To investigate the extent of long-term chronic pain relief for fibromyalgia from escalating doses of intravenous lidocaine infusions offered at a pain management clinic.

Study Design

This study was completed by conducting a retrospective chart review at a pain management clinic. The charts were selected by searching for fibromyalgia (FM) patients that were treated with IV lidocaine. The specific inclusion and exclusion criteria are listed in Table 3. A total of 74 patients were selected for the study. The protocol for the IV lidocaine infusions involved a gravity drip over 90 minutes with continuous vital sign monitoring. Most of the patients returned every two months for their infusions while others returned >100 days. The first dose administered was 5.0 mg/kg and escalating doses were administered based on the patient's preference. At each visit, various variables were collected from the patients. These included pain scores before and immediately after infusion, subjective assessment of percentage off change in pain, and other baseline demographics.

Inclusion Criteria	Exclusion Criteria
Diagnosis of FM	Missing outcome data
IV lidocaine treatment	Fewer than 3 infusions
	Protocol deviation
	Treatment occurred >3 years ago

Table 3: Participant Inclusion and Exclusion Criteria for Study 3.

Study Results

Long-term pain relief was reported as the patient's subjective impression of reduction in pain duration and intensity. The mean duration of pain relief for the 7.5 mg/kg dose of lidocaine was 14.05 days (Fig. 1). The mean duration of pain relief for the 5.0 mg/kg dose was 8.68 days (Fig. 1). The longest duration of pain relief for 7.5 mg/kg was 90 days, while the longest for 5 mg/kg was 49 days. Long-term lidocaine responders were defined as those with >25% pain relief for >14 days. Of the 74 patients, 25.8% were classified as long term responders after receiving 5.0 mg/kg dose of lidocaine. After receiving 7.5 mg/kg of lidocaine, 45.5% of the patients were considered long term responders. There was a statistically significant difference between the number of responders for the two infusion doses (P=0.022).

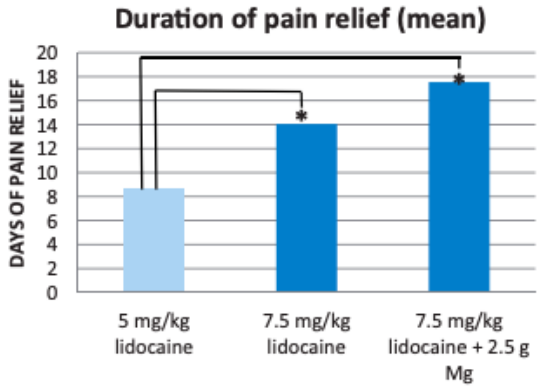

Figure 1: Average duration of pain relief for Study 3.

Study Critique

This study was a retrospective chart review on the long-term benefit of IV lidocaine infusions for patients with fibromyalgia. However, the study lacked strength because it was a

retrospective chart review rather than an RCT. The retrospective study over RCT meant that the lack of a control group allowed for biases in the study. Recall bias from the long period before data collection presents challenges to the conclusions. Additionally, there is limited documentation regarding the reasons why the number and dose of infusions differed among patients. This lack of information resulted in a decreased sample size. The authors recommended a randomized, double-blind, placebo-controlled study to investigate the role of IV lidocaine infusions in the treatment of fibromyalgia-related pain.

	Study #1	**Study #2**	**Study #3**
Study type	RCT	Retrospective	Retrospective
Patients, N	34	233	74
Primary Interest	Chronic neuropathic pain	Chronic pain (neuropathic vs non-neuropathic)	Fibromyalgia
Measurement of improvement	**Average pain intensity** Pain Interference Scale LEEDS Sleep Evaluation Hospital Anxiety Scale Hospital Depression Scale Impression of Change EQ-5D health outcome	Pain duration & intensity	Pain duration & intensity
# of lidocaine infusions	1	1 for everyone 2-3 infusions based on patient preference	Varied between patients
Confounding Variables	Pain >7 years 80% diabetic neuropathy Dose based on Pt weight	Incomplete/missing charts Allowed to continue other pain medications	Recall bias
Statistical significance	No	N/A	Yes
Clinical significance	Maybe initially post-infusion, but not long-term	Yes	Yes

Table 4: Overview of all three studies examined for analysis.

Discussion

Of the three studies analyzed, there was one randomized control trial (RCT) and two retrospective studies. The RCT, Moulin et al., showed no statistically significant impact on the intensity and duration of patient pain when compared with the control group that was given a placebo infusion (RR 0.17, 95% CI 0.50 to 0.84, p=0.61). In contrast, the retrospective studies showed that the IV lidocaine infusion did improve pain for a portion of the patients, some of whom elected to continue the infusions due to the beneficial effects. The results from Iacob et al. were categorized as percent reduction at seven days post IV lidocaine infusion. Of the 233 patients, 41% were defined as having benefitted, which means they reported pain reduction seven days after infusion. Those who reported pain reduction after the first infusion were more likely to follow-up for the second infusion when compared to those who did not benefit (92% vs three weeks, and 8% for three or more. Wilderman et al. showed the mean duration of pain relief for the 7.5 mg/kg dose of lidocaine was 14.05 days. After receiving 7.5 mg/kg of lidocaine, 45.5% of the patients were considered long term responders. Long-term lidocaine responders were defined as those with >25% pain relief for >14 days. Overall, the RCT showed no difference in pain for those receiving IV lidocaine while the two retrospective studies presented clinically meaningful benefits.

The three studies outlined varied based on their design, strengths/weaknesses, and biases. The first important comparison between the studies is the research design, specifically the 36%, p<0.001). After the first infusion, 40% had benefits for one to two weeks, 16% for two of the three studies analyzed, there was one randomized control trial (RCT) and two retrospective studies. The RCT, Moulin et al., showed no statistically significant impact on the intensity and duration of patient pain when compared with the control group that was given a placebo infusion (RR 0.17, 95% CI 0.50 to 0.84, p=0.61). In contrast, the retrospective studies showed that the IV lidocaine infusion did improve pain for a portion of the patients, some of whom elected to continue the infusions due to the beneficial effects. The results from Iacob et al. were categorized as percent reduction at seven days post IV lidocaine infusion. Of the 233 patients, 41% were defined as having benefitted, which means they reported pain reduction seven days after infusion. Those who reported pain reduction after the first infusion were more sample size and participant diagnoses. Moulin et al. was our most reliable study due to the nature of an RCT. However, a limitation of this study was the very small sample size of only 34 participants. A

majority of these patients reported specifically diabetic neuropathic pain for more than seven years. The aim of the study was to focus on chronic neuropathic pain in general, rather than only diabetic neuropathies. The reliability of the Moulin et al. is strong, but the sample size and characteristics of the patients presents limitations to their findings. Inversely, the Iacob et al had the largest sample size of 233 participants mostly with non-specified neuropathic pain, chronic regional pain syndrome, and migraines/headaches. Iacob et al. compared to Moulin et al. had more participants and a greater variety of chronic pain diagnoses. Wilderman et al. was solely focused on 74 patients with a diagnosis of fibromyalgia. Regardless, the study design of Moulin et al. outweighs the retrospective nature of both Iacob et al. and Wilderman et al.

The purpose of the three articles identified was to determine the extent of pain reduction for patients receiving the IV lidocaine infusions. The researchers quantified this outcome in various ways as outlined in Table 4. Moulin et al. focused on the mean pain intensity at four weeks for the experimental and placebo group as well as comparing pre-treatment to post-treatment pain reduction. Iacob et al. only looked at the percent of participants that were categorized as having benefited rather than specific pain scores. Wilderman et al. focused on length of duration of pain relief instead of numerical pain scores. The differing outcomes present challenges to producing a conclusion about the long-term effects of IV lidocaine on chronic pain. Iacob et al. and Wilderman et al. both focused on percent of patients with pain relief at a certain number of days rather than quantifying that pain relief.

Each of the studies used different IV lidocaine infusion doses and frequencies of administration. Moulin et al. administered the IV lidocaine at 5 mg/kg in 250 mL of normal saline once throughout the study. Iacob et al. gave the infusions at a rate of 1000 mg/h for up to 30 minutes as tolerated. Wilderman et al. administered the following doses of IV lidocaine: 5.0 mg/kg/dose and 7.5 mg/kg/dose. The different doses present variables to cross comparing the outcomes of the studies. Moulin et al. discussed the possibility of IV lidocaine analgesia occurring within a very narrow therapeutic index. They stated that participants may not have achieved a serum level high enough to experience the benefits of the infusion. Additional research is needed to determine the long-term pharmacokinetics of lidocaine and the appropriate dose for chronic pain relief.

One of the benefits of blinded RCT studies, such as Moulin et al, is the reduced effects of bias on the results. The patients are not aware of whether they are receiving the intervention or a placebo, meaning their results are less likely to be skewed in favor of the new treatment. The retrospective studies are not considered at the same level of quality because there is more room for confounding variables and bias. With the way that the Wilderman et al. study was conducted, there was a strong possibility of recall bias affecting the results, because the patients who improved are more likely to remember the results of the intervention.

This literature review was conducted with specific inclusion and exclusion criteria to keep the focus on the most common forms of chronic pain and excluding studies with cancer-related pain and post-surgical pain. However, as this is a relatively new treatment for chronic pain, there was a limited number of quality studies at the time of this review. The limited number resulted in including retrospective studies, which limits the effectiveness of the review and the ability to compare data most effectively.

While the results were mixed on the statistical significance of lidocaine infusions treating chronic pain, it is worth noting that statistical significance does not necessarily correlate with clinical significance. Meaning, Moulin et al. found that statistically, the treatment made little difference, but clinically it could be considered significant to the individual patients who found relief in the infusions.

Conclusion

The widespread misuse of opioid medications has led to an epidemic of avoidable addictions and deaths from overdose. The dire consequences of opioid misuse mean that every alternative treatment for pain relief needs to be thoroughly researched. Lidocaine infusions have very little risk of side effects, which leads to the discussion of the risks versus the potential benefits, as each patient that finds the therapy helpful is a patient that is able to avoid the risks of opioid medications and addiction. Lidocaine infusions are also a viable option for providers who are uncomfortable prescribing any opioids in light of the epidemic, but who still want to give their patients relief from debilitating pain.

This literature review showed that there is very little research done on the potential benefits of IV lidocaine infusions in treating non-cancer chronic pain. Randomized Control

Trials (RCT) are the gold standard study, but researchers can't justify the cost and time of performing a RCT without evidence from retrospective studies, literature reviews, etc. With such a novel and promising treatment, there is a great need for more quality research into lidocaine infusions for pain relief.

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