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ORIGINAL RESEARCH

Intravenous Lidocaine for Treatment of Chronic Pain: A Retrospective Cohort Study

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Introduction: Neuropathic pain is a widespread problem with a big impact on quality of life. The currently used drug regimens are often insufficiently effective or cause – sometimes unacceptable – side effects. Intravenous lidocaine could be an alternative treatment, by blocking spontaneous depolarization and hyperexcitability in upregulated sodium channels in nociceptors. Research so far has shown varying results but the treatment protocols differed a lot and follow-up was usually short. In our hospital, lidocaine infusions have been applied for many years in a unique treatment protocol consisting of a relatively high dose of lidocaine (1000 mg) administered over 25 hours. Our aim is to share information on both the efficacy and safety of this treatment schedule.

Methods: We conducted a retrospective cohort study in all patients who received a lidocaine infusion between January 2014 and January 2018. The standard infusion protocol consists of a total of 1000 mg lidocaine administered intravenously during 25 hours (40 mg/hour). Pain diagnoses were stratified into 15 groups, in agreement with diagnoses used in daily practice. Effectiveness of the treatment was classified as effect or no effect based on the description found in the chart.

Results: We included 282 patients, with a median age of 58 years and 64% of whom were female. Patients with myofascial pain syndrome, peripheral (mono)neuropathy, small fiber neuropathy and vascular disease benefited most. Patients with cancer pain, postherpetic neuralgia, chemotherapy-induced neuropathy and radicular pain showed the least pain improvement. There were no serious adverse events.

Conclusion: In selected patients, lidocaine infusions may be a safe and efficacious treatment for chronic neuropathic pain. More prospective research is needed to further determine the optimal dosing, duration and interval of lidocaine infusion therapy, and to better understand in which specific patient categories this treatment is most beneficial.

Keywords: chronic pain, neuropathic pain, intravenous, lidocaine

Introduction

Neuropathic pain is a widespread problem, with a worldwide prevalence of 6.9–10%[1] and a negative impact on the health-related quality of life.[2–6] Patients with neuropathic pain are more likely to suffer from comorbidities such as anxiety, depression and sleep disorders.[7–10] The most often prescribed medications against neuropathic pain at the moment are (strong) opioids, antidepressants and anti-epileptics,[11] but their efficacy is disappointing, with a number needed to treat (NNT) ranging between 3.6 and 7.7.[12] Up to three quarters of patients who use anti-neuropathic pain medication report moderate to severe pain despite their treatment.[6–8,13–15] Many patients consequently never accomplish complete or even sufficient pain relief, or do not tolerate adequate doses of medication owing to side effects.[16,17] Apart from the direct impact on quality of life, neuropathic pain also places a socio-economic burden on both patient and society, leading from loss of mobility, ability to work and sometimes even the ability to function independently in daily life.[18]

Currently, the group of elderly patients (>65 years) is large and still growing. Because of numerous comorbidities (eg diabetes mellitus), degeneration and inflammation of the nervous system, (post-)infectious diseases and side effects of medical treatment (eg chemotherapy), it can be assumed that the percentage of older adults with neuropathic pain is higher than in younger adults. Pain in this group is also more likely to be underdiagnosed, and hence undertreated. This can have multiple negative consequences on people's quality of life and overall health, for instance immobilization, falls,

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sleep disorders and depression. Moreover, when elderly people are treated with anti-neuropathic pain medication or opioids, they are considerably more at risk of developing (serious) side effects and interactions.[19,20]

An alternative pharmacological treatment is systemic (intravenous) lidocaine, which is a local anesthetic and sodium channel blocker. One of the possible pathophysiological mechanisms of the development of neuropathic pain is upregulation of sodium channels in the cell membrane of nociceptors, which causes spontaneous firing and neuronal hyperexcitability. Systemically administered lidocaine could diminish these neuronal discharges by selectively blocking the involved type of sodium channels, possibly explaining the analgesic effect on neuropathic pain.[21,22] Normal nerve conduction is not affected in this process. Lidocaine also possesses anti-inflammatory properties and is an NMDA-receptor antagonist.[23] This, too, may contribute to the reduction of central and peripheral excitability.

Over recent years, various research studies have been conducted in animals and humans, both prospective (placebo-controlled) and retrospective, to evaluate the effect of systemic lidocaine in neuropathic pain conditions of multiple origins.[24–40] The dosing, infusion time, outcome measures, patient populations and treatment schedules used in these studies differ enormously. The reported results vary from no benefit to quite a large decrease in pain scores, or a large percentage of responders. Furthermore, the incidence of reported side effects also shows a big variation. Most studies contained a small patient population and the effect was usually evaluated only until a few hours after the infusion,[25,27,28,30,35,36] whereas there are clues that some patients may experience maximum benefit only after 24 hours post-infusion.[41] Another issue concerns the adequacy of the used doses of lidocaine. Research by Wallace et al suggests that the therapeutic plasma level of lidocaine is between 1 and 5 μg/mL. Lower levels do not have a significant analgesic effect, and higher levels pose an increased risk of adverse effects (both cardiovascular and neurologic).[35,42] Other studies also suggest a larger effect when using higher doses (eg 5 mg/kg instead of 1 or 2 mg/kg).[25,28,34] From this, one could hypothesize that administering a higher dose of lidocaine using a lower infusion rate might achieve the desired pain relief with minimal side effects. No literature exists concerning the question of whether the duration of infusion is an independent variable.

Based on multiple RCTs and retrospective studies, lidocaine can at least be considered to be a potentially valuable alternative in the treatment of chronic neuropathic pain in selected patients. When infusion rates are kept within certain limits, it seems to be well tolerated and safe. Most studies have included very specific subgroups of patients, and evaluated the effect within short intervals of the actual infusion. What it lacking is a clear image of the (long-term) effects of systemic lidocaine in a heterogeneous group of patients, such as one would encounter in a typical pain clinic, and a better idea of which subgroups of those patients are more likely to respond well.

In our pain clinic, lidocaine infusions have been used in chronic neuropathic pain patients for many years now. Based on experiences of fellow pain practitioners, a scheme is used in which a total of 1000 mg is administered during a period of 25 hours (infusion rate of 40 mg/hour).

In this retrospective cohort study, we studied the analgesic effect of this 25-hour intravenous administration of lidocaine in a large heterogeneous population of neuropathic pain patients. Further, we evaluated the tolerability and incidence of adverse events associated with the aforementioned treatment schedule.

Methods

Data Collection

Patients who received one or more lidocaine infusions between January 2014 and January 2018 were included in this retrospective chart review. Patient number, date of birth, sex, date of first infusion and number of total infusions were automatically extracted from the electronic medical file and anonymized. All further information was manually extracted from the individual charts. Pain diagnosis, earlier treatment and any other relevant details were – when provided – found in the records of the first outpatient (intake) visit. Narrative notes at follow-up visits or phone calls (typically after four or more weeks) regarding the quality and duration of pain relief afterwards were used to assess the effect of the lidocaine infusion(s). From the clinical infusion records, any side effects experienced during or after the lidocaine infusions were evaluated.

Lidocaine Infusion Protocol

In our teaching hospital, the infusion of lidocaine in patients with intractable neuropathic pain has been a treatment option since 2002. A unique dosing schedule is used, which combines a relatively large total dose of lidocaine (1000 mg) over a relatively long period of time (25 hours). This schedule was composed like this because earlier clinical experience in other hospitals had shown that adequate pain relief was only achieved with high doses of lidocaine, but the (toxic) side effects with a high infusion rate were often a limiting factor.

The infusions are administered on a regular ward, with vital signs (heart rate and blood pressure) measured upon arrival (before the infusion) and then every 8 hours. In the startup of this treatment, patients were admitted to the ICU for constant monitoring. This showed no hemodynamic or arrhythmogenic adverse events. No plasma concentration is measured and the dose is independent of patient weight and other characteristics. This means that every patient receives the same dose during the same period of time. A few exceptions to this rule exist, since a few patients have experimentally noticed pain relief only after longer infusion than 25 hours. These patients receive the infusion for a period of 48 hours.

After the treatment, a telephone checkup is scheduled 4–6 weeks later. In patients who experience relief of symptoms, the infusion is repeated in a minimum of 6 weeks after the last one.

Pain Diagnosis

Our patients experience a very wide range of pain symptoms, which are not always easily categorized. We chose to divide all patients into subgroups according to pain diagnoses, consistent with the way in which they are encountered in daily practice (instead of more generalized classifications such as those provided by the IASP[56]). A total of 15 groups was distinguished in this cohort. Pain diagnoses were, if not explicitly noted in the intake record, formulated based on the description, location and circumstances of the symptoms. The first reviewer (SH), who had no treatment relationship with the patients, categorized the pain diagnoses. This was checked for approval by the second reviewer (JC), an experienced pain specialist (Table 1).

Pain Relief

The occurrence of pain and/or symptom relief after the infusion was extracted from the reports of follow-up visits and phone calls, which were usually of a narrative character. Sometimes numeric pain scores were noted, but since these were not systematically used, they were only used as guidance in the interpretation of the amount of pain relief and not used as

Table 1 Pain Diagnosis

	N	%
Cancer pain	7	2.5
Central pain	9	3.2
CRPS	8	2.8
Diabetic neuropathy	21	7.4
FBSS	9	3.2
Myofascial pain syndrome	19	6.7
Neuropathic pain n.o.s.	54	19.1
Neuropathy after chemotherapy	10	3.5
Pain n.o.s.	30	10.6
Peripheral (mono)neuropathy (other)	18	6.4
Postherpetic neuralgia	12	4.3
Postoperative/posttraumatic neuropathic pain	49	17.4
Radicular pain	20	7.1
Small fiber neuropathy	11	3.9
Vascular disease	5	1.8
Total	282	100

a measurement in itself. Both SH and JC judged the patient descriptions of the effects of the infusion, and classified them as effect or no effect. Descriptions containing very doubtful or variable reports of pain relief were scored as no effect. Also, taking into account the possible (placebo) effect of the high hopes and expectations that patients may have when undergoing a new treatment, reports of pain relief only after the first and/or second infusion and not after subsequent infusions were also considered as no effect. Pain relief duration shorter than 3 days was considered to be no effect. Some patients did not explicitly report pain relief, but did report feeling better or being able to function better in daily life, or just reported feeling "a big difference". In these cases, under the condition that the improvement in well-being and functioning was reported not just once but repeatedly, the effect was considered to be present and this was assessed as effect. Missing reports – in the case of one to three infusions – and cases with no follow-up were classified as unclear. The treating pain specialist would regularly schedule patients for three infusions to evaluate the effect, and only in case of clinically significant effect was it continued. Nevertheless, all unclear effect reports (also when more than infusions were administered) were stratified into the no effect group, to prevent overestimation of benefit in these patients.

Statistics

Demographics and information concerning the number of lidocaine infusions and the encountered pain diagnoses and side effects were presented as frequencies, percentages or a median number and interquartile range. Treatment effects were stratified by pain diagnosis, and presented as the percentage of patients within each group experiencing clinically significant pain relief.

Ethics

The study was performed in accordance with the principles stated in the Declaration of Helsinki. The local Institutional Review Board (IRB) of the Deventer Hospital (Deventer, The Netherlands) gave approval for the data collection and further performance of the study. The reference number of this approval is ME21-34. All patient data were collected retrospectively by one of the authors and were anonymized; hence there was no need for patient consent.

Results

A total of 282 patients received lidocaine infusions during the period between January 2014 and January 2018. The majority of these patients were female (64%) and the median age was 58 years (Table 2).

The patients in the group called "Pain n.o.s." had pain diagnoses such as chronic abdominal or back pain, localized or generalized pain without a clear cause, chronic arthritis-related pain, etc.

In total, 107 patients (37.9%) reported a clinically significant benefit of the treatment and 108 patients (38.3%) clearly noted no effect (Figure 1). There were no significant differences between males and females. Of all patients with missing, confusing, variable or conflicting effect documentation (n=67), who hence were assessed as if no clinically significant benefit had occurred, a total of 20 patients (29.9%) received more than three infusions. Patients who seemed to benefit most were those with a diagnosis of myofascial pain syndrome (55.0%), peripheral (mono)neuropathy n.o.s. (55.6%), small fiber neuropathy (54.5%) and vascular disease (60%), although the last group was very small (five patients). The

Table 2 Demographics and Number of Infusions

		N	Median (IQR)	%
Sex	Male	101		35.8
	Female	181		64.2
Age (years)			58 (48–69)	
Infusions (no.)	1	122		43.3
	2	36		12.8
	3	33		11.7
	>3	91		32.3

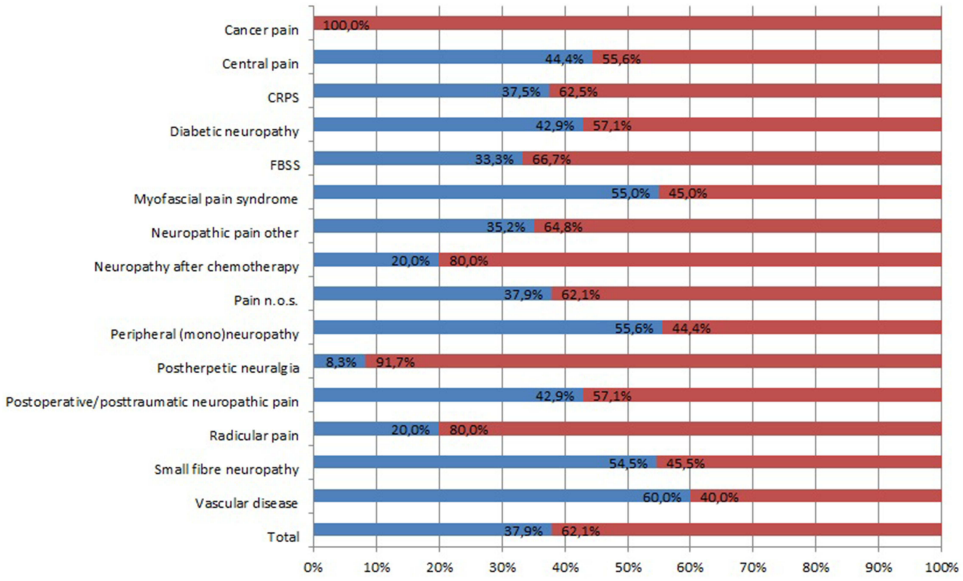

Figure 1 Effect per group.
Notes: Blue bar = effect; red bar = no effect.

least benefit was found in the groups with cancer pain (0%), postherpetic neuralgia (8.3%), chemotherapy-induced neuropathy (20.0%) and radicular pain (20.0%).

Adverse effects were reported by 12 patients (4.3%), and were all mild and transient (Table 3). In six cases the infusion was stopped because of the side effects, whereas the other six cases did not require cessation. The reported allergic reactions comprised one case of small bumps in the neck area and one case of pruritus over the entire body.

Discussion

Lidocaine infusion gives clinically significant pain relief in patients with chronic pain, with the largest treatment effect seen in myofascial pain syndrome, peripheral neuropathies, small fiber neuropathy and vascular disease-related pain. For patients with cancer pain, post-chemotherapy neuropathic pain or postherpetic neuralgia, only a small number reported pain relief. The infusions are safe, with only 4.3% of patients reporting side effects, none of which was serious or long-lasting.

Our data suggest an overall report of pain relief of just under 40%, with a large range of 0–60% in different pain diagnosis groups. A small underestimation of benefit could be possible, given the fact that almost 30% of patients who were stratified as having experienced no effect (because of unclear data) received more than three infusions. The treating pain practitioners in our clinic usually only continue the infusions when patients report symptom relief.

Table 3 Adverse Effects

	N	Infusion Continued?	
		Yes	No
Allergic reaction	2	1	1
Bradycardia	1	1	0
Chest pain	1	0	1
Nausea	3	3	0
Paresthesias	1	0	1
Tiredness	1	1	0
Other	3	0	3
Total	12	6	6

The high response in the group of patients with myofascial pain syndromes is remarkable, and data to compare the efficacy of systemic lidocaine in this group are not available. In some studies, myofascial pain syndromes are mentioned as a separate group, but either the group size is very small (n=5[44]) or sufficient data on the effect are missing.[41] Two studies using lidocaine 5% patches for treating myofascial pain syndromes found beneficial results, but the question is whether the mechanism is the same as with systemic lidocaine treatment. We have no clear explanation for why this group seems to respond so well to the lidocaine infusions, especially because the underlying etiologies of myofascial pain are greatly heterogeneous, but it may have to do with the anti-inflammatory properties of the drug.

Patients with peripheral (mono)neuropathy and small fiber neuropathy showed an above-average response to lidocaine as well. We hypothesize that this may be due to the direct blocking effect of lidocaine in several locations of abnormally behaving nerve tissues and/or preventing their excessive activation.[45–53,56] Given the very small number of patients in the group with vascular pain, their response to lidocaine should be evaluated in a larger number of patients in order to interpret the meaning of this finding.

Opioid-refractory cancer pain was shown to be treated more effectively with intravenous lidocaine than with a placebo in a study by Sharma et al.[52] Also, a systematic review by Lee et al[53] showed potential benefits of lidocaine in cancer pain. Our data cannot confirm these findings, since none of the patients with cancer pain reported any pain relief. This may be coincidental, due to the very small number of patients in this group (five), or perhaps the dosing scheme has something to do with the difference in effect.

A remarkable finding in our population is the small effect that lidocaine treatment seems to have on radicular pain, including postherpetic neuralgia. This is in contrast with some earlier studies,[30,32] including a recent placebo-controlled study on postherpetic pain,[54] which found a significantly lower VAS and decrease in analgesic rescue medication when lidocaine infusions were administered. Previous studies on postherpetic neuralgia, however, show only a moderate decrease in allodynia[25] (not specifically tested by us) and benefit from lidocaine 5% patches.[55] The latter was considered to arise from the systemic effects of the lidocaine, because of the large surface area of the patches, but nevertheless is a completely different treatment and hence, in our opinion, not comparable.

To our knowledge, this is one of the largest studies, or even the largest study, to evaluate the effect of intravenous lidocaine infusion in neuropathic pain patients. Furthermore, it is the only study so far assessing the clinical effect in a heterogeneous study population, which enables the extrapolation of treatment effects to daily clinical pain practice. By stratifying treatment results on pain diagnosis, we were able to assess which pain patients would be likely to benefit most from lidocaine treatment. The described pain diagnoses for which lidocaine infusions were indicated resemble those reported in the literature. Moreover, a unique dosing scheme using a high total dose during a long infusion period, maintaining a low infusion rate, is used. No other study, to date, has reported the effects of a similar or comparable dosing scheme.

Compared to most other used doses, our patients receive a relatively large total dose, but over a much longer period of time. The reason for this combination is the hypothesis (based on preliminary clinical experience) that a certain minimum dose is necessary for efficacy, but that a high infusion rate can cause a higher incidence of adverse effects. In our practice, and in most referred studies, no plasma concentrations were measured or mentioned. Therefore, it remains unclear whether any analgesic effect of lidocaine is concentration dependent and, following from this, whether any ineffectiveness could possibly be due to an inadequate plasma concentration. An RCT conducted by Wallace et al,[42] studying pain thresholds and allodynia in response to various stimuli during lidocaine infusion titrated to different plasma concentrations in a step-up manner, shows a beneficial effect of lidocaine only with the highest plasma concentration. This suggests that there may be a minimal plasma concentration needed to reach an analgesic effect. Because of the step-up protocol, this may equally be related to the total cumulative dose of lidocaine.

Our data suggest that the used dose of 1000 mg has a clinical benefit in approximately 40% of our total patient group – with some diagnosis groups attaining even more frequent relief of pain relief (up to 60%). This is comparable with the findings of quite a few other studies, although most of them use lower total doses and (much) higher infusion rates. Given the very low incidence of adverse effects (4.3%) and the even lower need for cessation of the treatment because of such effects (2.2%), it may be feasible to administer the same (or a lower) dose in a shorter time frame without a negative impact on the pain-relieving effect. From the perspective of cost-effectiveness, patient comfort and paucity of clinical care and beds, this would be desirable.

A possible explanation for the low incidence of adverse effects in our population is the low infusion rate of 40 mg/hour, leading to very little toxicity (or at least very few symptoms of toxicity). Hutson et al[41] demonstrated a direct relationship between a higher infusion rate and a higher incidence of adverse effects. These findings seem to match our data.

Owing to the retrospective nature of this study and chart review, the diagnosis classification and treatment effect evaluation were not standardized. From oral information provided by the treating pain specialists, we know that, in general, patients who are offered intravenous lidocaine treatment suffer from chronic pain (mostly neuropathic, but also non-neuropathic or of mixed/unclear origin) which has not been adequately treated by an array of first and second line treatments (medication or other). Sometimes initial treatment was not enough to alleviate the pain, sometimes it was stopped because of unacceptable side effects and sometimes a combination of these two scenarios occurred. In a small minority of patients, lidocaine was offered before some more common treatments were tried, because of reasonable expectation of unacceptable side effects. This was the case in some very old and fragile patients, but also in a few patients with young children and/or a responsible job who could not afford to be less alert or unable to drive, or to suffer any comparable interfering side effects. It was not documented clearly when these – alternative – indications for lidocaine treatment were used, and thus we could not take this into account when evaluating the data.

For better understanding of which types of pain respond best to intravenous lidocaine treatment and to determine the optimal dosing and infusion rate, a larger, prospective study would be needed. The insights derived from our data provide a glimpse of information that can be used to guide future research in this field. For daily practice, some of the more distinct results could also help to guide clinical decision making until we have more definitive answers from high-quality prospective studies.

Disclosure

The authors report no conflicts of interest in this work.

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