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REPORT OF ORIGINAL INVESTIGATIONS

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

Lidocaïne intraveineuse pour la prise en charge de la douleur neuropathique périphérique chronique : une étude randomisée contrôlée

Dwight E. Moulin, MD · Patricia K. Morley-Forster, MD · Zameer Pirani, MD · Cathy Rohfritsch, RN · Larry Stitt, MSc

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Abstract

Purpose *Neuropathic pain, resulting from injury to the peripheral or central nervous system, is due to upregulation of aberrant sodium channels with neuronal hyperexcitability. Lidocaine blocks these channels and several studies show that intravenous (IV) lidocaine infusion provides significant relief in patients with chronic peripheral neuropathic pain in the short term (for up to six hours). Our objective was to determine if IV lidocaine provides significant pain relief and overall improvement in quality of life in the longer term (for up to four weeks).*

Methods *This single site randomized double-blind, crossover trial compared IV lidocaine infusion (5 mg·kg^{-1}) with active placebo infusion containing diphenhydramine (50 mg) in patients with chronic neuropathic pain of peripheral nerve origin of at least six months duration. The primary outcome was average pain intensity reduction from IV lidocaine relative to placebo at four weeks post-infusion. Secondary outcome measures included parameters of physical function, mood, and overall quality of life.*

Results *We enrolled 34 subjects in this trial—mostly with painful diabetic neuropathy and post-herpetic neuralgia. There were no significant differences between IV lidocaine and placebo infusions at any time point involving any of the outcome measures. Mean (standard deviation) pain intensity at week 4 for the placebo and lidocaine groups were not different [6.58 (1.97) vs 6.78 (1.56), respectively; between-group difference, 0.17; 95% confidence interval, − 0.50 to 0.84].*

Conclusion *We found no significant long-term analgesic or quality of life benefit from IV lidocaine relative to control infusion for chronic peripheral neuropathic pain.*

Trial registration *clinicaltrials.gov (NCT01669967); registered 22 June, 2012.*

Résumé

Objectif *La douleur neuropathique, résultat d'une lésion du système nerveux périphérique ou central, est due à l'augmentation de canaux sodiques aberrants accompagnée d'une hyperexcitabilité neuronale. La lidocaïne bloque ces canaux et plusieurs études ont démontré qu'une perfusion intraveineuse (IV) de lidocaïne offrait un important soulagement à court terme (pour une durée maximale de six heures) aux patients atteints de douleur neuropathique périphérique chronique. Notre objectif était de déterminer si la lidocaïne IV procurait un soulagement significatif de la douleur et une*

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D. E. Moulin, MD (✉)
Department of Clinical Neurological Sciences and Oncology, Western University, London, ON, Canada
e-mail: dwight.moulin@lhsc.on.ca

P. K. Morley-Forster, MD · Z. Pirani, MD
Department of Anesthesia and Perioperative Medicine, Western University, London, ON, Canada

C. Rohfritsch, RN
Lawson Health Research Institute, London, ON, Canada

L. Stitt, MSc
Statistical Services, London, ON, Canada

amélioration globale de la qualité de vie à plus long terme (pour une durée maximale de quatre semaines).

Méthode *Cette étude randomisée croisée à double insu et mono-site a comparé une perfusion de lidocaïne IV (5 mg·kg^{-1}) à une perfusion de placebo actif contenant de la diphenhydramine (50 mg) chez des patients atteints de douleur neuropathique chronique provenant du système nerveux périphérique et durant depuis au moins six mois. Le critère d'évaluation principal était la réduction moyenne de l'intensité de la douleur procurée par la lidocaïne IV par rapport au placebo à quatre semaines post-perfusion. Les critères d'évaluation secondaires comprenaient divers paramètres pour mesurer la capacité physique fonctionnelle, l'humeur et la qualité de vie globale.*

Résultats *Nous avons recruté 34 patients pour cette étude, la plupart souffrant de neuropathie diabétique douloureuse et de névralgie post-herpétique. Aucune différence significative n'a été observée entre les perfusions de lidocaïne IV et de placebo, quel que soit le point de mesure dans le temps, pour aucun de nos critères d'évaluation. L'intensité de la douleur moyenne (écart type) à la semaine 4 était similaire dans les groupes placebo et lidocaïne [6,58 (1,97) vs 6,78 (1,56), respectivement; différence intergroupe, 0,17; intervalle de confiance 95 %, − 0,50 à 0,84].*

Conclusion *Nous n'avons trouvé aucun bienfait significatif sur l'analgésie à long terme ou la qualité de vie d'une perfusion de lidocaïne IV par rapport à une perfusion témoin pour soulager la douleur neuropathique périphérique chronique.*

Enregistrement de l'étude *clinicaltrials.gov (NCT01669967); enregistrée le 22 juin 2012.*

Neuropathic pain (NeP) arising from a lesion or disease affecting the somatosensory system[1] remains a challenging clinical problem because the pain is often severe and disabling.[2] Population-based studies indicate that the prevalence of NeP is in the range of 7–10% based on validated screening tools for NeP.[3-5] These data suggest that at least 2,000,000 Canadians suffer from this disabling condition and this mandates the need for effective pharmacologic interventions. The efficacy of certain antidepressants, anticonvulsants, opioid analgesics, and miscellaneous agents have been established in systematic reviews[6-8] and several evidence-based guidelines for the management of NeP have been developed.[9-11] Nevertheless, these studies consistently show that less than 50% of patients achieve adequate pain control in the short term and a recent prospective observational outcome study of neuropathic pain patients showed that only about a quarter attained clinically significant improvement in pain and function in the long-term at 12 month follow-up.[12] There is therefore a pressing need for alternate treatment strategies. Systematic reviews and meta-analyses of the systemic administration of local anesthetics to relieve NeP provide good evidence that intravenous (IV) lidocaine infusions at a dose of 5 mg·kg^{-1} provide significant pain relief compared with placebo for up to six hours after infusion and also show an excellent safety profile.[13,14] Nevertheless, evidence of benefit beyond six hours is scant. A crossover trial in painful diabetic neuropathy showed significant benefit relative to placebo eight days following lidocaine infusion but this trial only involved 15 patients and may have been under-powered.[15]Another study also involving 15 patients with painful diabetic neuropathy showed significant reduction in pain intensity relative to a placebo infusion at both 14 and 28 days after infusion, but this was an enriched protocol design where all subjects declared benefit from previous monthly lidocaine infusions for at least one year.[16] Despite this low quality evidence, there has been a dramatic increase in the provision of IV lidocaine infusions for neuropathic pain in Ontario over the past ten years. In 2007, 20 physicians administered IV lidocaine infusions on 366 patients while in 2017, 127 physicians performed this procedure on 15,039 patients.[17] These findings provide the rationale for a rigorous randomized-controlled trial to determine the long-term outcome of the role of IV lidocaine infusion in the management of chronic neuropathic pain.

Methods

Design and setting

We conducted a single site randomized, double-blind, crossover trial to test the hypothesis that IV lidocaine infusion will provide significant pain relief and overall improvement in quality of life for up to four weeks in patients with chronic neuropathic pain of peripheral nerve origin relative to placebo infusion. We recruited participants from September 2011 to August 2015 from the Neuropathic Pain Clinic of St. Joseph's Hospital in London, Ontario. This academic tertiary referral pain clinic saw patients one day a week with a volume of approximately 70 new patients annually. Participants were also recruited from a single advertisement in the local community paper. We received approval for the trial from the Office of Research Ethics on behalf of Western University's Research Ethics Board (17 March, 2011) and all patients provided written informed consent before enrollment. We also obtained a no objection letter from

Health Canada (Control # 147703) for approval of this study since IV lidocaine in the management of neuropathic pain is off-label. This study is registered at clinicaltrials.gov (NCT01669967).

Participants

We screened all patients aged 18–80 yr who were seen in the Neuropathic Pain Clinic at St. Joseph's Hospital. This weekly clinic was triaged for neuropathic pain by a trained research nurse (C.R.), but the final diagnosis was not made until a full medical assessment by the principal investigator (D.E.M.). Participants were therefore recruited by C.R. and D.E.M. Inclusion criteria were: 1) chronic neuropathic pain of peripheral nerve origin of at least six months duration, 2) reported average pain intensity of 5 or greater on a 0–10 numerical rating scale over three days, and 3) a score of 4 out of 10 or greater on the DN4 questionnaire to validate the presence of neuropathic pain.[18] Exclusion criteria were: 1) presence of clinically significant cardiac disease such as unstable angina, congestive heart failure, or poorly controlled arrhythmia, 2) poorly controlled seizure disorder, 3) cognitive or language barriers, 4) history of allergy to amide local anesthetics or to diphenhydramine, 5) prior treatment with a local anesthetic infusion, 6) use of recreational drugs in the last two years, and 7) neuropathic pain due to cancer, complex regional pain syndrome, fibromyalgia, or mixed pain associated with chronic neck or back pain. Complex regional pain syndrome type 1 due to a soft tissue injury and fibromyalgia were excluded because it remains controversial whether these entities constitute neuropathic pain.[1]

Interventions

Randomization and concealment of allocation were pharmacy-controlled. Eligible participants were randomly assigned in a 1:1 allocation ratio to either IV lidocaine or active placebo infusion in an unblocked unstratified manner. The sequence of drug treatment was assigned by the unblinded hospital pharmacy, using a web-based random number generator (www.randomizer.org). To ensure concealment of allocation and blinding of the investigators and the study nurse, infusions were compounded by the hospital pharmacy and provided as clear solutions which were identical in appearance.

We anticipated that painful diabetic neuropathy with type 2 diabetes mellitus and comorbid obesity would be a common diagnosis among our participants. Intravenous lidocaine infusions were therefore given at a dose of 5 $mg{\cdot}kg^{-1}$ using lean body weight[19] in 250 mL of normal saline and the active placebo infusion consisted of diphenhydramine 50 mg in saline with both infusions given over 45 min. Diphenhydramine has previously been used as an active placebo to increase the likelihood of subject blinding since it mimics the most common side effects of lidocaine—drowsiness and dizziness.[20] Participants were crossed over to the opposite infusion six weeks later.

Continuous electrocardiogram, oximetry, and automated, non-invasive blood pressure were recorded every five minutes during the infusion and for 30 min thereafter. Participants continued all their usual medications including analgesic medications during the trial. Participants were given a diary for data collection at the end of each infusion and the research nurse called participants on a weekly basis as a reminder to enhance data collection. The diary from the first phase of the study was collected upon return for the second infusion and the diary for the second phase was collected during a follow-up visit.

Outcome measures

Our primary outcome measure was the difference in average pain intensity (numerical rating scale 0–10) between lidocaine infusion and active placebo infusion at four weeks post-infusion. Average pain intensity was obtained at baseline, six hours, and then then daily throughout the four weeks of each phase of the study. The overall average pain intensity at the end of each week was a composite of the mean average pain intensity obtained daily throughout each week of the study. The numerical rating scale (0–10) is a commonly used primary outcome measure in neuropathic pain trials and is sensitive to change.[21] Secondary outcome measures were based on core outcome domains established by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT).[22] The IMMPACT guidelines mandate that outcome measures include pain, physical functioning, mood, overall quality of life, a measure of global satisfaction with treatment, and documentation of adverse events. Secondary outcome measures were obtained at baseline, days 1, 3, 7, 14, 21, and 28 in each phase of the study as follows: Pain Interference Scale of the Brief Pain Inventory for Physical Functioning, Hospital Anxiety and Depression Scale for Mood, EQ-5D health outcome instrument for quality of life, Patient Global Impression of Change for Global Satisfaction, LEEDS Sleep Evaluation questionnaire for sleep quality,[23] and adverse events were documented according to a standard list of common side effects associated with analgesic trials and categorized as mild, moderate, or severe. Participant demographics, pain characteristics, and baseline analgesics including opioid dosing and co-interventions such as transcutaneous electrical nerve stimulation,

acupuncture, and massage therapy were also documented. Oral analgesic management was not altered during the course of the study.

Statistical analysis

Between-group comparisons were made using a mixed model analysis of variance. The mixed model incorporates terms for treatment assignment (lidocaine *vs* placebo), sequence (lidocaine first *vs* placebo first) and period (first and second) as fixed effects. Patients were included as a random effect allowing for the comparison of lidocaine and placebo as a within subject effect. Through the use of a mixed model, data from subjects who completed the first period only could be incorporated into the model.[24] Least squares between-group differences and their 95% confidence intervals (CI) are presented along with the associated *P* values. Missing daily values for average pain intensity within periods were imputed using last observation carried forward and then averaged over the week. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Sample size was based on a systematic review and meta-analysis comparing active drug and placebo.[13] In this study, the weighted mean difference in pain intensity on a 0–100 scale was − 10.60 (CI, − 14.52 to − 6.68). Based on this outcome and a standard deviation (SD) of approximately 1.5 for a crossover trial,[24] 26 subjects are required to detect such a difference at the 0.05 two-sided level of significance with 90% power.

Results

Participants

Figure 1 shows the flow of participants through the trial. The first patient was recruited on September 30, 2011 and the last patient was followed-up September 25, 2015. Of the 105 participants who were eligible for the study, 34 were randomized and included in the intent to treat analysis. Two participants dropped out after the first phase of the study because of lack of efficacy. Sixteen subjects (47.1%) were randomized to lidocaine first. Table 1 shows participant demographics, pain characteristics, and baseline analgesics. Notably, the mean pain duration was more than seven years and the majority of the participants presented with painful diabetic neuropathy (79.4%). Most participants were treated with two or more adjuvant analgesics for their NeP and the majority were also treated with opioid analgesics with mean and median morphine equivalent daily doses of 195 and 180 mg respectively (Table 2). The mean total body weight (SD) was 94.8 (25.4) kg. The mean lean body weight (SD) and lidocaine dose (SD) were 61.8 (12.9) kg and 309.3 (64.8) mg, respectively.

Outcome measures

Table 2 shows outcome measures at four weeks post-infusion. For the primary outcome measure (average pain intensity), the difference between lidocaine and placebo infusions at the end of week four (0.17, 95% CI, − 0.50 to 0.84) was not significant ($P = 0.61$). Similarly, there was no significant difference in any of the secondary outcome measures at the same time point. No difference in the outcome measures at any of the other measured time points including six hours post-infusion were observed. Finally, there were no significant differences between any of the time points and baseline values (eTable 1, available as Electronic Supplementary Material [ESM]). There were no differences in the reported frequency or severity of side effects between the lidocaine and placebo groups (eTable 2, available as ESM), and all participants remained hemodynamically stable through all infusions (eTable 3, available as ESM). There was a very modest drop in mean arterial pressure in the active placebo group relative to lidocaine at 50–70 min following initiation of infusions but this was not clinically significant. Similarly, there was a very modest drop in heart rate at 40 min but again this was not clinically significant. The most common side effects of treatment at 24 hr post-infusion (those reported at 24 hr but not prior to infusion) were drowsiness, nausea, abdominal discomfort, and light-headedness (Table 3).

Discussion

In this randomized placebo-controlled trial involving patients with peripheral neuropathic pain, we did not show significant long-term analgesic benefit of IV lidocaine infusions. This finding does not support the utility of IV lidocaine infusions at a standard dose of 5 $mg \cdot kg^{-1}$ for the long-term management of intractable peripheral neuropathic pain. Furthermore, we did not observe any short term analgesic benefit or any improvement in physical functioning, mood, or overall quality of life.

There is a strong rationale for the consistently reported short term analgesic benefit of IV lidocaine for chronic neuropathic pain including painful diabetic neuropathy and post herpetic neuralgia given its short serum half-life of 120 min.[25] Lidocaine has multiple mechanisms of action including inhibition of voltage-gated sodium channels, blockage of N-methyl-D-aspartate receptors, and anti-

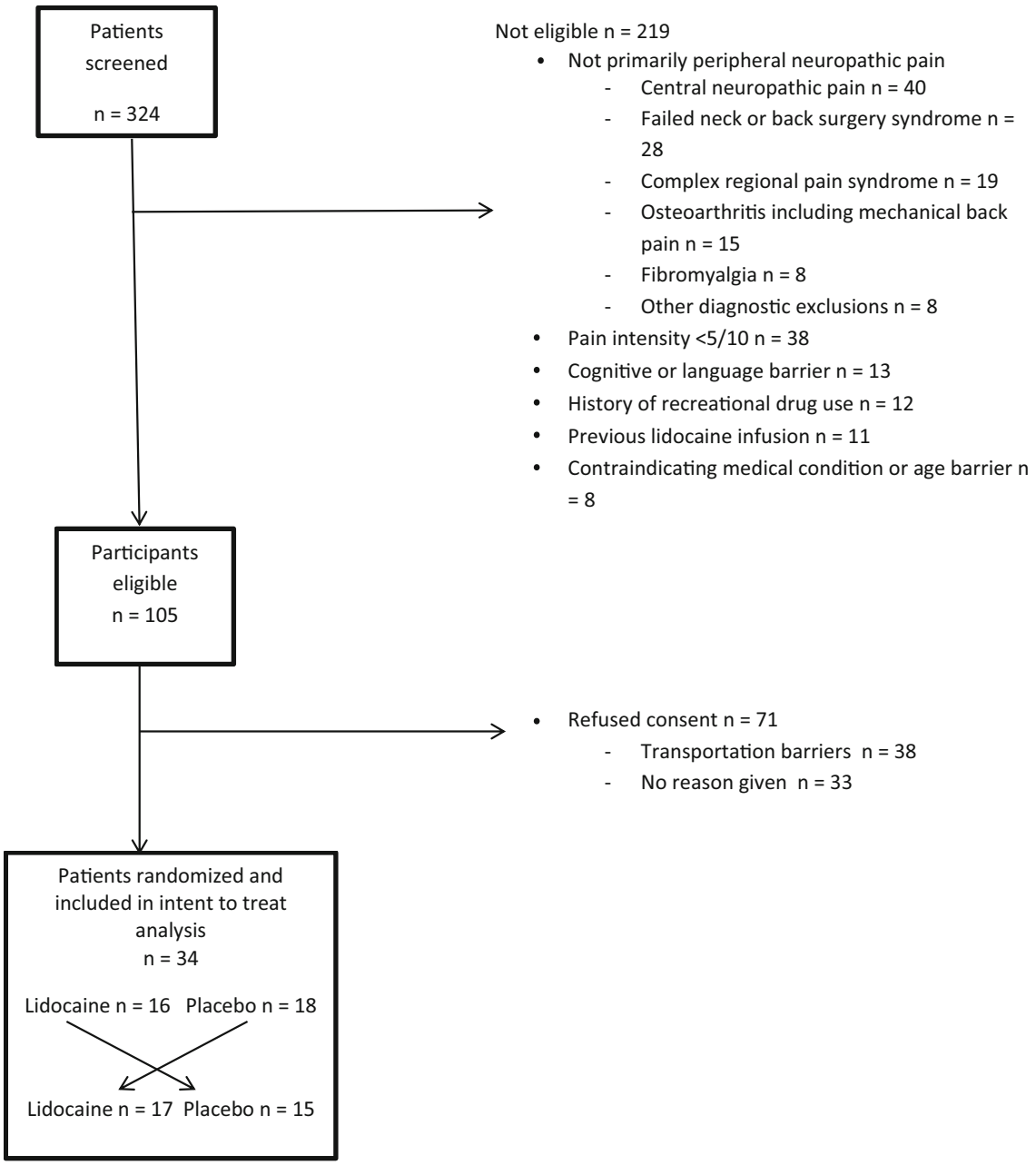

Figure 1 Flow of participants through the trial

inflammatory effects.[26] More specifically, lidocaine preferentially blocks up-regulated aberrant sodium channels that are responsible for neuronal hyperexcitability after nerve injury.[27] These aberrant sodium channels are very sensitive to lidocaine blockade at plasma concentrations that do not affect normal nerve conduction.[28] These plasma concentrations are within the therapeutic range of 1.3–3.7 $\mu g \cdot mL^{-1}$ for both IV lidocaine infusion at 5 $mg \cdot kg^{-1}$ and for epidural infusions.[29,30]

The rationale for long-term analgesic benefit extending over weeks following lidocaine infusion is weaker. Nevertheless, there is evidence that lidocaine blocks aberrant sodium channels in the dorsal horn of the spinal cord following spinal cord injury.[31] As well, the anti-inflammatory effects of lidocaine may inhibit glial activation in the central nervous system.[32] These latter two mechanisms of action may decrease the role of central sensitization in the generation of chronic peripheral NeP.[33] Our use of diphenhydramine as an active placebo may have preserved study blinding and prevented the observation of placebo analgesic responses.[34]

Table 1 Participant demographics, pain characteristics, and baseline analgesics (n = 34)

Age, mean (SD)	58 (12)
Pain duration, months (SD)	89 (57)
Average pain intensity (0–10) (SD)	6.5 (1.2)
Sex, male	22 (65%)
Diagnoses	
Painful diabetic neuropathy	27 (79%)
Postherpetic neuralgia	4 (12%)
Other	3 (9%)
Analgesics	
None (%)	3 (9%)
Analgesic antidepressants (%)	23 (68%)
Anticonvulsants (%)	22 (65%)
Cannabinoids (%)	4 (12%)
Non-pharmacological (%)	1 (3%)
Opioids (%)	25 (74%)
Opioid dose (MED)	
Mean (SD)	195.5 (±163.4)
Median [interquartile range]	180 [73–240]

MED = morphine equivalent dose; SD = standard deviation

Limitations

This study was carried out in a tertiary care pain clinic where patients are referred after long-term intractable pain. This is reflected in the mean pain duration of greater than seven years in our study participants. As shown in Table 2, these patients were treated with multiple adjuvant analgesics as well as aggressive opioid regimens without adequate pain control. There is evidence that chronic pain patients who are resistant to high dose opioid treatments have a poor outcome due to comorbid mood disorders and risk factors for substance abuse.[35] Nevertheless, our patients had only mild levels of mood impairment at baseline on the Hospital Anxiety and Depression Scale (Table 3) and patients with a history of substance abuse were excluded from study participation. Independent of these factors, patients seen at an earlier stage of their disease may have a better outcome. In addition, approximately 80% of our participants had painful diabetic neuropathy and there is evidence from quantitative sensory testing that different neuropathic pain syndromes show different somatosensory profiles that may benefit from specific mechanism-based treatment approaches.[36,37] Acknowledging that painful diabetic neuropathy is the commonest cause of chronic neuropathic pain worldwide,[38] it is possible that other kinds of neuropathic pain, including central neuropathic pain syndromes and entrapment neuropathies of shorter duration, might show a better analgesic response to IV lidocaine.

Serum levels of lidocaine and its metabolites were not measured during the infusion. A clinical pharmacokinetic study by Ferrante *et al*. suggested that the mechanism of analgesia to IV lidocaine may not be based on the usual concentration-effect relationship, but is instead characterized by sudden pain relief over a narrow concentration range.[39] This is reflected in a very narrow therapeutic index where plasma concentrations of lidocaine exceeding 5 $\mu g \cdot mL^{-1}$ commonly lead to systemic toxicity.[27] This was our rationale for using lean body weight at 5 $mg \cdot kg^{-1}$ for lidocaine dosing since the mean total body weight in our predominantly obese participant group was 94.8 kg (range 47.6–143.9). Nevertheless, some participants may not have achieved a high enough serum concentration of lidocaine to obtain benefit even at six hours post-infusion.

Table 2 Primary and secondary outcome measures: intravenous lidocaine *vs* active placebo (n = 34)

	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 3 Frequency of most common (> 30%) individual and severe side effects at 24 hr post-infusion

Side effect	Any occurrence		Severe side effect	
	Lidocaine (n = 34)	Placebo (n = 34)	Lidocaine (n = 34)	Placebo (n = 34)
Fatigue	21 (61.8%)	23 (67.7%)	6 (17.7%)	3 (8.8%)
Drowsiness	17 (50%)	23 (67.7%)	3 (8.8%)	3 (8.8%)
Dry mouth	18 (52.9%)	18 (52.9%)	5 (14.7%)	8 (23.5%)
Constipation	16 (47.1%)	17 (50.0%)	4 (11.8%)	1 (2.9%)
Decreased sex drive	16 (47.1%)	14 (41.2%)	8 (23.5%)	7 (20.6%)
Impaired memory	14 (41.2%)	13 (38.2%)	2 (5.9%)	2 (5.9%)
Visual blurring	14 (41.2%)	12 (35.3%)	1 (2.9%)	2 (5.9%)
Insomnia	12 (35.3%)	13 (38.2%)	3 (8.8%)	3 (8.8%)
Confusion	11 (32.4%)	13 (38.2%)	1 (2.9%)	0 (0.0%)
Light-headedness/dizziness	12 (35.3%)	12 (35.3%)	1 (2.9%)	0 (0.0%)

Conclusion

Patients with longstanding neuropathic pain especially due to diabetic neuropathy are unlikely to respond to IV lidocaine infusion in the long term. More studies using IV lidocaine infusions are required to determine the short-term and long-term benefits in neuropathic pain patients with less intractable disease and different pain syndromes.

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