Original Article

Lidocaine for Neuropathic Cancer Pain (LiCPain): A Pilot Randomized Controlled Trial

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Abstract

Context. Extended continuous subcutaneous infusion of lidocaine for neuropathic cancer pain is currently used in clinical practice.

Objective. To determine the feasibility of conducting an adequately powered, multisite, double-blind, parallel group, titrated dose, randomized controlled trial of continuous subcutaneous infusion of lidocaine versus placebo in palliative care patients with neuropathic cancer pain.

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Methods. Adults with neuropathic cancer pain were randomized to receive lidocaine hydrochloride 10%w/v (3000 mg/30 mL) diluted in sodium chloride 0.9% or sodium chloride 0.9% as a continuous subcutaneous infusion titrated daily for 72 hours. The dose increased from 1 to 2 mg/kg/h, capped at 120mg/hour (2800mg/day, rounded down).

Results. Seventeen participants were recruited over 54 months. There was a 93% [95%CI 88%−98%] completion rate of study medication and procedures meeting the predefined feasibility criteria. Eighty-eight percent of participants completed 72 hours of study medication. Treatment-emergent adverse events were infrequent and generally mild or moderate nervous system, cardiac and vascular abnormalities. There were no electrocardiogram abnormalities. Rapid titration from 1 to 2 mg/kg/h was tolerated. Both intervention and control groups demonstrated a reduction in pain intensity with no significant difference.

Conclusion. This pilot demonstrates that a phase III clinical trial of extended continuous subcutaneous infusion of lidocaine for neuropathic cancer pain is feasible and provides important insights into modifications required to improve recruitment. Serum levels and relative safety suggest higher lidocaine doses could be cautiously evaluated. As the only prospective trial we are aware of to date, this trial informs clinical use of subcutaneous lidocaine infused over days. J Pain Symptom Manage 2025;70:267−277.

Key Words

Palliative care, lidocaine, pain control, cancer pain, randomized controlled trial, feasibility

Key Message

This randomized controlled pilot found a continuous subcutaneous infusion of lidocaine for neuropathic cancer pain is feasible and provides important insights into trial design modification required to improve recruitment. As the only prospective trial we are aware of to date, it informs clinical use of subcutaneous lidocaine infused over days.

Introduction

There is urgent need for improved interventions to manage neuropathic cancer pain. Pain with a neuropathic component affects up to 39% of people with advanced cancer, despite advances in treatment.[1] People with neuropathic cancer pain are significantly more likely to receive strong opioids, anticonvulsants, and antidepressants yet have worse physical, cognitive and social function.[2]

New management strategies are required to reduce the impact of neuropathic cancer pain. There is level 1 evidence for systemic lidocaine infusion to improve chronic neuropathic pain.[3] However, despite its use in clinical practice,[4−7] few randomized controlled trials have evaluated systemic lidocaine in people with advanced cancer.[8,9] The evidence to date is inconclusive on the benefit of systemic lidocaine in this population. Systematic review shows a signal of benefit for a short intravenous infusion of lidocaine.[8] A randomized controlled trial of subcutaneous lidocaine given over 5.5 hours was inconclusive,[9] possibly due to subtherapeutic doses. To our knowledge, there are no randomized controlled trials evaluating an extended continuous infusion of lidocaine, however observational studies show benefit of infusions between 1 and 240 days.[4,6,10,11]

The purpose of this trial was to determine the feasibility of conducting an adequately powered randomized controlled trial of continuous subcutaneous infusion of lidocaine versus placebo in palliative care patients with neuropathic cancer pain.

Methods

Design

This pilot study comprised a phase II double-blind randomized controlled parallel group pilot of subcutaneous infusion of lidocaine hydrochloride or placebo over 72 hours for neuropathic cancer-related pain, a pharmacokinetic substudy, and a qualitative substudy of patients' and carers' experiences.

The trial and pharmacokinetic substudy are reported here according to the Consolidated Standards of Reporting Trials extension for randomized pilot and feasibility trials Checklist.[12] In-depth details are included in the published protocol paper[13] and the Australian New Zealand Clinical Trial Registry (ACTRN12617000747325), with summarized methods presented here. The qualitative substudy will be reported subsequently.

Ethics

All participants provided written informed consent. This study was approved by the Sydney Local Health District (Concord) Human Research Ethics Committee 2019/ETH07984 and the University of Technology Sydney ETH17-1820. A major protocol amendment was undertaken dated June 2022, which included reducing the analgesic pretreatment and expanding the definition of neuropathic cancer pain to include those who meet the International Association for the Study of Pain (IASP) definition of neuropathic pain.[14]

Population

Participants were recruited from 5 palliative inpatient units in Sydney, Australia, between July 2019 and January 2024. The units comprised a total 107 beds and approximately 2500 new admissions per year. Key inclusion criteria were neuropathic cancer pain with a worst pain score ≥4 out of 10 on the Brief Pain Inventory-Short Form, and an adequate trial of opioid and adjuvant analgesia. Neuropathic pain was defined as a Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale score ≥12 or meeting the IASP definition for neuropathic pain. Pain was related to cancer or its treatment. Key exclusion criteria were liver failure, chronic kidney disease stage V, cardiac failure, heart block, cardiac ischemia, Stokes-Adams syndrome, heart rate and blood pressure abnormalities, seizure, delirium and medications which interact with lidocaine (see also Supplementary Table 1).

Potential participants were invited to take part upon admission to the palliative care unit and during regular screening at each site.

Intervention

Participants were randomized 1:1 to receive the intervention or control, with both treatment groups receiving best practice standard of care. Intervention: Lidocaine hydrochloride 10% w/v (3000 mg/30 mL) diluted in sodium chloride 0.9%; Control: Sodium chloride 0.9%.

Study drugs were prescribed as a continuous subcutaneous infusion titrated every 24 hours to effect and adverse effects. The dose started at 1 mg/kg/hour (maximum 120 mg/hour). The participant was assessed for efficacy and toxicity on days 2 and 3, and the dose was increased by 0.5 mg/kg/hour every 24 hours to a maximum of 2 mg/kg/hour or 120 mg/hour (whichever is lower) unless the pain was well controlled, or toxicity was present. The dose remained the same if the patient's average and worst pain score in the last 24 hours was ≤3/10 on the Brief Pain Inventory (BPI-SF). A new or increased toxicity was managed according to the protocol, which could include treatment of the symptom, dose reduction or cessation of infusion. After 72 hours (on day 4), the infusion was ceased.

Concomitant Care

The best practice standard of care included continuation of prescribed continuous and breakthrough analgesic (without further dose change) in both groups of the study.

Outcomes

The primary outcome was the proportion of study medication and procedures completed ("nonmissing data"). Baseline data was collected on day 1. Efficacy, toxicity and serum concentration were collected on days 2, 3 and 4 with followup data collected on days 8, 15 and 29. The ideal (100%) 'nonmissing data' was defined as having completed study medication and procedures on a daily basis by assigning a "1" for all completed assessments; and a '0' for incomplete assessments, or where the participant had withdrawn or ceased the infusion, from baseline to day 4. This total was expressed as a proportion of the maximum score of 42. A "nonmissing data" proportion of more than 80% was considered feasible, while a confidence interval which included 60% was considered unfeasible. This outcome was chosen to ensure that participant fatigue and clinical instability would not be a barrier to completing this trial.

Secondary outcomes included the feasibility of conducting the trial, preliminary efficacy, toxicity, health outcomes and health service utilization associated with the intervention, and the relationship between lidocaine serum concentration and dose/efficacy/toxicity (Supplementary Tables 2 and 3).

Sample Size and Recruitment

Fleming's 2-stage trial design was used to determine the sample size based on an acceptable completion rate of 80% and an unacceptable completion rate of 60%.[13] This calculation generates a range of values. A mid-value was selected taking into consideration that sufficient feasibility data is required to inform a future phase III study. The null hypothesis was that the true completion rate is 0.6 was tested against a 1-sided alternative. In the first stage, 17 participants were accrued. As there were 15 or more responses (participants with a completion rate where the confidence interval included 80% and excluded 60%) from 17 participants, the study was stopped and the null hypothesis rejected. If there were 10 or fewer responses in these 17 patients, the study was to be stopped for futility. If there were between 10 and 15 responses, 19 additional patients would have been accrued for a total of 36. This design yielded a type I error rate of 0.05 and power of 0.8 when the true response rate was 0.8.

Blinding and Allocation

All participants, study staff, clinicians and investigators except the sponsor national manager and statistician were blinded. Treatment for each participant was allocated in a 1:1 ratio.

Pharmacokinetic Sampling and Analysis

Participants in the pharmacokinetic substudy had steady-state blood samples collected at baseline (Day 1) and between 20-24 hours after dose titration. Samples were frozen at −80°C then transported at 4°C to the laboratory. Samples were analyzed using a validated high performance liquid chromatography (HPLC) assay[15] to estimate lidocaine and metabolite concentrations.

Data Analysis

The primary analysis was conducted on a modified intention to treat basis, that is according to the participants' randomization for participants who received at least 1 dose of study treatment. Safety analysis was conducted according to the allocation for all participants who received at least 1 dose of study treatment.

The analysis was repeated in the per protocol set which comprised of all participants who received 72 hours of study treatment; according to the participant's actual allocation.

Pharmacokinetic data were reported using descriptive statistics. Categorical data were summarized using proportions and compared between treatment groups using risk ratios and Pearson's chi-squared tests. Continuous outcomes were described using mean and standard deviation for normally distributed data, and medians, maximum and minimum for nonnormally distributed data. Between groups comparisons were conducted using generalized linear models. Unless otherwise stated, results are presented as mean (standard deviation).

Results

Demographics

Seventeen participants were randomized from 124 screened (Fig. 1). The mean age of participants was 64.1 (11.2) years, mean weight 70.8 (23.3) kg and 77% were female. The mean worst pain score at baseline was 7.8 (1.2), with a mean daily oral morphine-equivalent regular opioid use of 189.2 (160.6) mg (Table 1).

Feasibility of Completion and Recruitment

Prescreening data identified that the most common reasons for exclusion were low pain severity (<4/10 worst pain on BPI-SF), inability to complete study assessments and inadequate analgesic pretreatment (Supplementary Table 4). Fourteen percent of screened participants were consented. It took 54 months to reach the sample size. The study was formally placed on hold for 7 months due to COVID-19, with a staggered return of sites after this. Two sites were added in 2020 and 2022.

The median time taken to perform eligibility visits was 85 minutes (range 20−300), baseline 75 minutes (range 20−160) and subsequent follow-up visits 40 minutes (range 20−175).

There was a 93% completion rate of study medication and procedures (95% confidence interval 88%−98%). Complete data sets were available for 29% of participants, and 82% had a 90% complete data set. The most commonly missed items were vital signs (1 to 2 sets missing in 24 hours) and missed individual questions in the BPI-SF and Neuropathic pain symptom inventory (NPSI) at cessation.

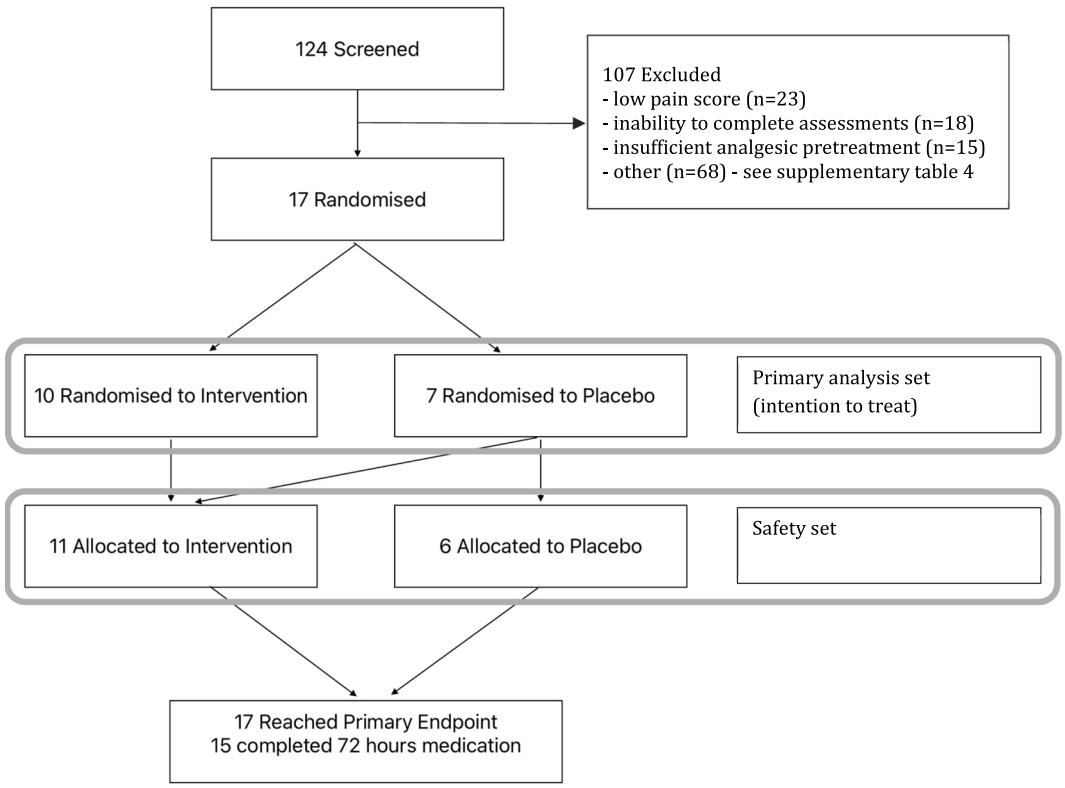


Fig. 1. CONSORT diagram.

Table 1
Participant Demographics

Characteristic	All n=17	Randomization Lidocaine n=10	Randomization Control n=7	*P* value
Age, years mean (SD)	64.1 (11.2)	64.9 (11.0)	62.9 (12.3)	0.73
Sex: female (%)	13 (77%)	8 (80%)	5 (71%)	0.68
Weight, kg mean (SD)	70.8 (23.3)	61.4 (14.9)	84.1 (27.7)	0.045
Primary Cancer (%)				
Colorectal	5 (29%)	4 (40%)	1 (14%)	0.25
Breast	5 (29%)	2 (20%)	3 (43%)	0.31
Lung	4 (24%)	2 (20%)	2 (29%)	0.68
Other gastrointestinal	1 (6%)	0	1 (14%)	-
Other urological	1 (6%)	1 (10%)	0	-
Metastatic sites of cancer (%) Bone	11 (65%)	7 (70%)	4 (56%)	0.59
Lymph nodes	8 (47%)	6 (60%)	2 (29%)	0.20
Lung	5 (29%)	4 (40%)	1 (14%)	0.25
Liver	5 (29%)	3 (30%)	2 (29%)	0.95
Other	3 (18%)	2 (20%)	1 (14%)	0.76
Charleson Comorbidity Index mean (SD)	7.2 (2.2)	7.2 (2.1)	7.2 (2.5)	0.96
Interpreter required (%)	2 (12%)	1 (10%)	1 (14%)	0.79
Usual language: English (%)	13 (77%)	8 (80%)	5 (71%)	0.68
Worst pain in 24 hours prior to baseline from 0−10 mean (SD)	7.8 (1.2)	8.1 (1.4)	7.3 (1.1)	0.21
Average pain in 24 hours prior to baseline from 0−10 mean (SD	5.5 (1.8)	5.5 (1.5)	5.6 (2.4)	0.94
Leeds Assessment of Neuropathic Symptoms and Signs ≥12 (%)	8 (47%)	6 (60%)	2 (29%)	0.20
Baseline oral morphine equivalent, mg mean (SD)	189.2 (160.6)	199.7 (188.1)	174.2 (123.6)	0.76
Baseline oral morphine equivalent				
≥200mg		3 (30%)	2 (29%)	0.95
60−200mg		3 (30%)	4 (57%)	0.26
≤60mg		4 (40%)	1 (14%)	0.25
Baseline RUG-ADL mean (SD)	4 (4−10)	7.4 (4.5)	6.0 (3.5)	0.50
AKPS mean (SD)	50(11.2)	48.0 (12.3)	52.1 (9.5)	0.40
Other pain management exposure				
Patient education (%)	9 (53%)	4 (40%)	5 (71%)	0.20
Pain diary (%)	4 (24%)	3 (30)	1 (14%)	0.45
Physiotherapy (%)	10 (59%)	6 (60%)	4 (57%)	0.91
Occupational therapy (%)	7 (41%)	5 (50%)	2 (29%)	0.38
Psychology (%)	4 (24%)	2 (20%)	2 (29%)	0.68
Music therapy (%)	1 (6%)	1 (10%)	0 (0%)	-

Eighty-eight percent (n=15) of all participants completed 72 hours of study medication (82% in the intervention group vs. 100% in the control group).

Preliminary Efficacy

There was no significant improvement in pain measure in the intervention compared with control group. The mean change in worst pain on the BPI-SF was −1.0 (1.25) in the intervention and −2.0 (2.77) in the control group (P=0.32). Other outcome measures are tabulated in Table 2 and Supplementary Table 5. Preliminary efficacy was also examined based on the per protocol set (Supplementary Table 6). This accounted for 2 participants who did not complete the intervention due to toxicity, 1 participant who was randomized to control but was allocated intervention; and 1 participant who was missing the BPI-SF on day four. Similar results were obtained in both sets.

Preliminary Toxicity

The safety analysis set comprised of 11 participants in the intervention group and 6 participants in the control group. There were 37 treatment-emergent adverse events (TEAE) experienced during the trial from baseline to cessation, 29 in the intervention and 8 in the control group (Table 3). Overall, nine (82%) people in the intervention and four (67%) in the control group experienced 1 or more TEAEs (P=0.48). These included 'possibly, probably or definitely related' adverse events (AE) events in both groups.

The most common TEAEs for the intervention group were tremor (n=3), ataxia (n=3) and fatigue (n=3). No changes in electrocardiogram (ECG) were seen. Four participants in the intervention group and 1 in the control group had changes in vital signs. Grade 3 (severe) or worse TEAEs occurred in 2 participants in the intervention group and 2 participants in the control group. The remaining adverse events were mild or moderate. There were no serious adverse events reported while on the intervention. Three participants in the intervention and 2 in the control group had adverse events resulting in reduced or discontinued study infusion.

Adverse events during follow-up, are tabulated in Supplementary Table 7. There were 4 serious adverse events of "neoplasm" leading to death: in the intervention group 1 occurred during follow-up and 2 were an incidental finding poststudy; in the control group 1

Table 2
Efficacy Measures

Outcome	Randomized: Lidocaine	Randomized:Control	Risk ratio	*P* value
From baseline to cessation	**Participants with improvement:**			
Number (%) of participants with improvement of	**N=10***	**N=7***		
Worst pain of ≥1 point on BPI-SF	6 (60%)	4 (57%)	1.05	0.91
Average pain of ≥1 point on BPI-SF	3 (30%)	5 (71%)	0.42	0.09
Worst pain reduced to ≤3 on BPI-SF	1 (10%)	3 (43%)	0.23	0.12
Number of breakthrough pain medications used	3 (30%)	2 (29%)	1.05	0.95
Number of participants with improvement of ≥1 point:	**N=9***	**N=7***		
Burning (superficial) spontaneous pain on NPSI (%)	3 (33%)	4 (57%)	0.58	0.34
Pressing (deep) spontaneous pain on NPSI (%)	2 (22%)	4 (57%)	0.39	0.15
Paroxysmal pain on NPSI (%)	4 (44%)	5 (71%)	0.62	0.28
Evoked pain on NPSI (%)	2 (22%)	4 (57%)	0.39	0.15
Paresthesia/Dysesthesia on NPSI (%)	3 (33%)	4 (57%)	0.58	0.34
Pain	**N=10***	**N=7***		
Worst Pain, median (min, max)	−1.00 (−3.00, 1.00)	−2.00 (−5.00, 2.00)		0.33
Average Pain, median (min, max)	0.00 (−3.00, 3.00)	−2.00 (−7.00, 1.00)		0.05
No. of breakthrough medications used, median (min, max)	1.00 (−5.00, 5.00)	1.00 (−2.00, 2.00)		0.95
Neuropathic Pain Symptom Inventory	**N=9***	**N=7***		
Total Intensity on Neuropathic Pain Symptom Inventory (out of 100)	2.00 (−17.00, 62.00)	−27.00 (−41.00, −1.00)		0.02
Burning (Superficial Spontaneous) Pain	0.00 (−9.00, 2.00)	−2.00 (−9.00, 6.00)		0.92
Pressing (Deep Spontaneous) Pain	0.00 (−5.00, 2.50)	−3.00 (−6.50, 0.00)		0.09
Paroxysmal Pain	−0.50 (−8.00, 0.50)	−1.00 (−10.00, 0.00)		0.59
Evoked Pain	1.17 (−3.33, 6.33)	−1.33 (−3.67, 1.67)		0.08
Paresthesia/Dysesthesia	0.00 (−2.50, 8.00)	−1.00 (−5.00, 0.00)		0.05
At cessation:				
Global impression of change (number)	**N=9***	**N=7***		0.31
very much improved	1 (11%)	0 (0%)		
much improved	1 (11%)	4 (57%)		
minimally improved	2 (22%)	2 (29%)		
no change	2 (22%)	1 (14%)		
minimally worse	0 (0%)	0 (0%)		
much worse	1 (11%)	0 (0%)		
very much worse	2 (22%)	0 (0%)		

*Number of participants randomized to lidocaine/control and had complete relevant data. One participant (lidocaine) had incomplete patient reported outcome data at day 4.

Table 3
Treatment Emergent Adverse Events

System Organ Class	Preferred Term	All Events (n=37)		Grade 3 or Worse (n=4)	
		Allocated to Lidocaine (n=11)	Allocated to Control (n=6)	Allocated to Lidocaine (n=11)	Allocated to Control (n=6)
Total number of adverse events		29	8	2	2
Nervous system disorders	Tremor	3 (27%)	0	0	0
	Ataxia	3 (27%)	0	0	0
	Dizziness	2 (18%)	0	0	0
	Paresthesia	2 (18%)	0	0	0
	Somnolence	2 (18%)	0	0	0
	Lethargy	1 (9%)	0	0	0
	Movement Involuntary	0	1 (17%)	0	0
General disorders and administration site conditions	Fatigue	3 (27%)	0	2 (18%)	0
	Hyperhidrosis	1 (9%)	0	0	0
	Injection Site Reaction	0	1 (17%)	0	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	2 (18%)	0	0	0
	Sore Throat	1 (9%)	0	0	0
Eye disorders	Blurred Vision	2 (18%)	0	0	0
Cardiac disorders	Palpitations	1 (9%)	0	0	0
	Sinus bradycardia	1 (9%)	0	0	0
	Sinus Tachycardia	1 (9%)	0	0	0
Vascular disorders	Hypotension	1 (9%)	0	0	0
	Hypertension	1 (9%)	1 (17%)	0	1 (17%)
Musculoskeletal disorders	Myalgia	0	1 (17%)	0	0
	Back pain	1 (9%)	0	0	0
Gastrointestinal Disorders	Abdominal Pain	0	1 (17%)	0	1 (17%)
	Nausea	0	1 (17%)	0	0
Ear and labyrinth disorders	Tinnitus	1 (9%)	0	0	0
Psychiatric Disorders	Confusion	0	1 (17%)	0	0
Infections and Infestations	Fever	0	1 (17%)	0	0

death occurred during follow-up (P=0.62). There was 1 serious adverse event of "confusion" in the control group.

Feasibility of Collecting Data to Inform Economic Analyses

Collecting data on health outcomes and resources used to inform economic analyses was feasible, including counting the number and length of hospital admissions and intervention use. Completeness and outcomes are shown in Table 4. The median baseline utility value was 0.50 (range 0.03-0.96). Three participants were admitted for 3 or 4 days and 1 outlier for 127 days. The remainder ranged from 9 to 67 days. The cost of lidocaine at the lead site was AUD$2.37 per 500mg, giving a median medication cost of $31 for the duration of the intervention.

Pharmacokinetic Data

Two of the 5 participants who consented to the pharmacokinetic substudy were allocated to intervention. Fig. 2 shows total and unbound lidocaine concentration data.

Intervention Exposure

Of those allocated to intervention, 4 were capped at 120mg/h, 3 reached 2mg/kg/h, and 4 had the dose reduced or ceased. The mean maximum dose in those who had a reduction in worst pain of ≥1 and received intervention was 1.5 (0.5) mg/kg/h compared with 0.9 (1.0) mg/kg/h in those who did not respond (P=0.25).

Discussion

To our knowledge, this is the only prospective Phase II randomized controlled trial (RCT) of an extended continuous subcutaneous lidocaine infusion. Other trials in people with cancer have investigated shorter subcutaneous[9] and intravenous[8] infusions of up to 5.5 hours. This study provides important feasibility data for a phase III clinical trial of extended subcutaneous lidocaine infusion. It provides systematically collected data informing lidocaine dosing and adverse effects in the clinical management of people with neuropathic cancer pain, adding to previous retrospective observational studies.[4–6] This study contributes significantly to the sparse literature prospectively evaluating subcutaneous infusions of lidocaine in people with neuropathic cancer pain.

Intervention Feasibility

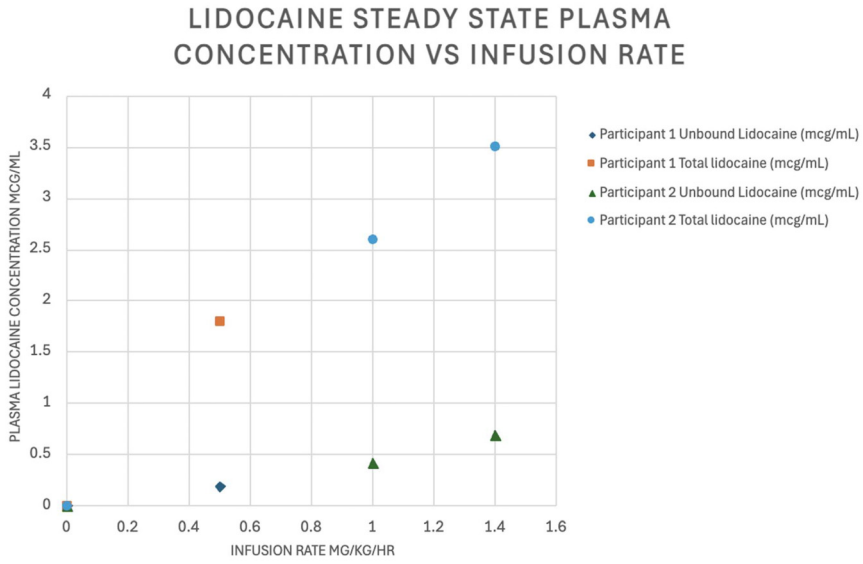
This study shows that it is feasible to complete a 72-hour infusion of subcutaneous lidocaine in people with neuropathic cancer pain, titrating daily from 1mg/kg/h to 2mg/kg/h with a maximum dose of 120mg/h. Eighty-eight percent of participants completed 72 hours of study medication. International use of lidocaine varies widely,[11] and this study adds to the evidence that this dose algorithm could be used in clinical practice. However, clinicians should note that there is insufficient evidence to use continuous subcutaneous lidocaine infusions for neuropathic cancer pain It should be considered if other evidence-based strategies are not suitable or in the context of a clinical trial. Any risk and benefit should be carefully assessed.

Few participants who consented to the pharmacokinetic study were randomized to intervention. Future trials might stratify for this substudy. An open label pharmacokinetic study with pain scores and toxicity correlation may further inform dosing. Consistent with other reported data,[5,9,10] serum lidocaine levels during this subcutaneous infusion appear to be lower than

Table 4
Health Outcomes, Resource Use and Costs

	Complete Data	Median	Range
Change in utility value (n=15)	88%	0.12	−0.34–0.36
Daily cost based on AR-DRG (AUD$) (n=16)	94%	1551.90	1246.19–1696.80
Length of stay (days) (n=17)	100%	23	3–127
Lidocaine use (mg) (n=17)	100%	6420	2000–8400
Change in RUG-ADL (n=17)	100%	0	−6–0
Change in AKPS (n=17)	100%	0	−20–20
Change in Pain interference (n=15)	88%	2.14	−1.14–5.00

Abbreviations: RUG-ADL = Resource Utilization Groups – Activities of Daily Living; AKPS = Australia-modified Karnofsky Performance Status; AR-DRG = Australian Refined Diagnosis Related Groups.



Infusion dose for 24h prior (mg/kg/h)	Unbound lidocaine (mcg/mL)	Total lidocaine (mcg/mL)	Participant	Treatment Emergent Adverse Events
0	<0.05	<0.1	1, 2, day 1	N/A
0.5	0.18	1.8	1, day 4	Increase in tremor and paresthesia from grade one to grade two together with perioral numbness on day two. Dose reduced from 1mg/kg/h to 0.5mg/kg/h at 2100 on day two. Symptoms were resolved by assessment at 1100 on day three. Pharmacokinetic data for days two and three are missing.
1	0.41	2.6	2, day 2	Grade one hypertension up to 169/68mmHg, increased from baseline of 152/79mmHg.
1.4 (capped at 120mg/h)	0.68	3.5	2, day 3	Grade one ataxia and an increase in tremor and lethargy from grade one to grade two.
1.4	0.69	3.5	2, day 4	

Fig. 2. Pharmacokinetics of lidocaine in 2 participants.

reported for intravenous infusions for cancer pain.[7,10,16] The highest lidocaine level was 3.5mcg/mL which is well below the 5 mcg/mL threshold for serious adverse effects.[17] Therapeutic levels of lidocaine for pain are not well established, however these fall within the quoted ranges of 2.5–3.5 mcg/mL[9] and 1.5–5 mcg/mL.[5] Participant 1 had a lower level of 1.8mcg/mL, in keeping with the lowered dose of 0.5mg/kg/h, below the starting dose. Given the relative safety demonstrated, higher lidocaine doses could be cautiously evaluated.

This pilot study was not powered for efficacy, however, both groups demonstrated a reduction in pain, with both the response rate and magnitude greater in the control group. The control response rate of 57% in this study was higher compared to other cancer pain studies which found placebo response rates of up to 27%.[18,19] Previous research has found that studies with blinded outcome assessor and concealed allocation have a higher placebo response.[20] Further research into whether specific features of this trial design, population or intervention contributed to the high placebo response may inform future cancer pain studies and delivery of the intervention.

Structured assessment found no significant difference in toxicity between lidocaine and placebo groups regarding the number of participants experiencing 1 or more TEAE or grade 3 or worse or serious AE. This study was not powered to compare AE between groups and caution is needed when interpreting this data to inform clinical practice. The rate of adverse events in both the intervention and control groups was higher than previously reported observational studies of extended subcutaneous lidocaine infusion,[6,7] and randomized controlled trials of shorter infusions.[21] Most adverse events in this study were of low severity. The most common were nervous system disorders. This study highlights the importance of daily structured clinical assessment and awareness of potential toxicities for early recognition of adverse effects for people on

lidocaine infusions in both clinical practice and future clinical trials. Cardiac and vascular events noted such as changes in heart rate and blood pressure may not be of clinical significance. Many AEs, including those graded serious, occurred in the follow-up or poststudy phase, which may be expected in this population given their comorbidity and frailty, and are unlikely to be attributed to the intervention itself.[22] All participants who died were in the follow-up or poststudy phase.

Despite daily monitoring, the lack of ECG changes suggests that it may be safe to conduct a future phase III trial at this dose with clinical assessment but without ECG monitoring. This is consistent with previous studies.[23] It is the first trial to prospectively record ECG in this population.

Trial Design Feasibility

Trial processes piloted were feasible for participants to complete with 93% completion of assessments and intervention, with the least compliance in vital signs and missed individual questions in the BPI-SF and NPSI at cessation. Key strategies to address this missing data may include limiting the collection of patient-reported outcomes to reduce the burden for participants and providing incentives for completeness of data collection.[24] Alternate methodological design such as the estimand framework could be considered to handle participants who cease the intervention or are lost to follow-up due to their underlying disease.[25]

The slow recruitment rate of this study highlights the challenges in recruiting to clinical trials in inpatients with neuropathic cancer pain. These are reflected in trials with similar populations.[26–28] It was noted that in addition to the reasons captured in prescreening, many inpatients were not screened due to cognitive impairment or being too unwell to complete assessments. There were unpredictable extended periods of challenging recruitment at each site due to staffing vacancies, competing clinical priorities and inpatient service constraints. A phase III trial will require modification to the design and recruitment strategy to ensure it is able to be completed in a reasonable timeframe and budget. Modifiable factors may include inpatient requirements and level of pretreatment of analgesics. Using the IASP definition of neuropathic pain[14] allowed inclusion of participants with clinician diagnosed neuropathic cancer pain who did not meet the LANSS cutoff, reflecting decision-making in clinical practice. Assessments could be adapted to allow more unwell people to participate. A future trial may consider evaluating this intervention in both neuropathic and nonneuropathic cancer pain, as in previous trials.[9,21] Alternate study designs may more efficiently guide practice, especially those which integrate systematic collection of evidence of efficacy into routine clinical care or provide an incentive to the control group through standardization of best practice care in both arms or a waitlist control design. The high placebo response rates in this study may be a helpful recruitment aid to future randomized trials.

Health economic data was feasible to collect. This population had a relatively poor quality of life compared with the Australian general population,[26,27] similar to other studies of neuropathic cancer pain.[28] The cost of the inpatient stay is high compared to the drug cost. Use of the intervention as an outpatient would significantly reduce this cost.

Limitations

This study shows that the intervention is feasible in this population, however selection bias may have excluded frailer people from this evaluation. The inclusion criteria are narrow, limiting the generalizability of this study but can be modified. Safety data from this study and other recent studies[9,23] may facilitate this. Covid-19 impacted the recruitment to this study directly due to clinical trial activity hiatus of up to 2 years and indirectly due to staff focus on clinical responsibilities, fewer research staff, reduced inpatient beds and increased reluctance for participants to be admitted to the hospital. Finally, the low uptake of the pharmacokinetic substudy limited the ability to correlate the clinical outcomes in these participants with a lidocaine level. Considering Hawley's recent study,[9] there is concern whether the lower-than-expected serum levels could impact the preliminary efficacy.

Conclusion

This pilot RCT demonstrates that a randomized controlled phase III clinical trial of continuous subcutaneous infusion of lidocaine for neuropathic cancer pain is feasible, however the current design would require modification to improve recruitment rates. It provides important insights into the design of clinical trials of lidocaine for people with neuropathic cancer pain and identifies areas to optimize, such as recruitment. As the only RCT to date of extended continuous subcutaneous infusion of lidocaine for neuropathic cancer pain, it adds to the evidence informing clinical use of lidocaine infusions, which are currently used in clinical practice allowing clinicians to better evaluate the risk and benefit.

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Supplementary Table 1
Population

Inclusion Criteria	Exclusion Criteria

• Age 18 years or more
• Capacity to provide informed consent
• Ability to complete study assessments and comply with the study procedures
• Participant is willing to be an inpatient for the duration of the trial
• Pain related to cancer or its treatment with a worst pain score of 4 or greater on an 11-point (0−10) numerical rating scale in the past 24 hours
• Patient's cancer may be solid tumor or hematologic
• Neuropathic component to pain which the clinician assesses to meet the International Association for the Study of Pain criteria for neuropathic pain which is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"[14] OR has a score of 12 or greater on the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS).[29] Mixed neuropathic/nociceptive pains are included as well as cancer induced bone pain which is considered to have a neuropathic component.[30]
• An adequate trial of opioid medication defined as titration to the maximum tolerated dose as limited by adverse effects or titration to at least a dose of 30mg/day oral morphine equivalent, for at least 24 hours
or inability to tolerate opioids (e.g., due to allergy)
• An adequate trial of at least 1 adjuvant analgesic defined as titration to the maximum tolerated dose as limited by adverse effects or titration to at least a dose of Amitriptyline 37.5mg, Duloxetine 30mg, Gabapentin 900mg, Pregabalin 150mg, Venlafaxine 60mg or equivalent, for at least 24 hours
or inability to tolerate any adjuvant analgesic listed above (e.g., due to comorbidity, medication interaction or previous adverse effects)
or inability to take oral medications (as determined by the treating clinician e.g., due to dysphagia)
or expected poor absorption of oral medications (as determined by the treating clinician, e.g., due to vomiting)
• Stable regular adjuvant analgesics, opioids, cannabinoids, antidepressants, anticonvulsants, benzodiazepines, paracetamol, nonsteroidal anti-inflammatory drugs and steroids for 24 hours. Transdermal opioids must have had stable dosing for 48 hours due to the extended time to reach steady-state. Short acting breakthrough opioid may be used as required.
	• Previous adverse reaction to lidocaine (lignocaine) or other amide-type local anesthetics such as prilocaine, mepivacaine or bupivacaine
	• Use of systemic lidocaine (lignocaine) infusion for analgesia within the 4 weeks prior to study entry at a dose greater than or equal to 1mg/kg/h intravenous or subcutaneous
	• Liver failure (Child class B or C, likely due to hepatic impairment)
	• Renal failure (eGFR <15ml/min/1.73m$^{2)}$
	• Cardiac comorbidity deemed a contraindication by the treating clinician including
	  ○ Symptomatic cardiac failure (New York Heart Association class II or greater[31] within the past year
	  ○ Heart block (first, second or third degree) at any time in the past ten years. Participants managed with a permanent pacemaker are not excluded
	  ○ Stokes-Adams syndrome
	• Cardiac abnormalities at time of screening
	  ○ Bradycardia less than 60 beats per minute at rest while awake
	  ○ Systolic blood pressure less than 100mmHg or greater than 160mmHg sitting
	  ○ Unstable angina or myocardial ischemia
	  ○ atrial or supraventricular tachycardia greater than 100 beats per minute at rest
	• Seizure episode within the past 4 weeks
	• Fluctuating level of consciousness or delirium as determined by the treating team
	• Acute porphyria
	• Current use of medications which may interact with lidocaine or impact its metabolism:[32] propranolol, phenytoin, amiodarone, metoprolol, nadolol, St John's Wort, donepezil, cimetidine, flecainide, fluvoxamine, dihydroergotamine, vernakalant, saquinavir, dronedarone, amprenavir, lopinavir, propofol, arbutamine, atazanavir, succinylcholine, dasabuvir, paritaprevir, cobicistat, hyaluronidase, delavirdine, fosamprenavir, etravirine, ombitasvir, quinidine, disopyramide, procainamide, tocainide, mexiletine, propafenone, encainide, moricizine, bupropion, telaprevir, penbutolol, rapacuronium, nevirapine, nitrous oxide, cisatracurium, indinavir, ritonavir
	• Participants who have participated in a clinical study of a new chemical entity within the 4 weeks prior to study entry
	• Pregnant or breastfeeding

Supplementary Table 2
Primary and Secondary Outcomes

Primary Outcome and Measure

The primary outcome is the completion rate of the study medication and procedures from day 1 to day 4. A completion rate of 80% or more of randomized patients is considered feasible and a completion rate of 60% or less is considered unacceptable.

Secondary Outcomes

Feasibility

- The number of eligible participants who are consented and randomized within the first 18 months from the lead site opening
- Recruitment to screening ratio
- Completion to screening ratio: the ratio of participants who complete all study medication and procedures from day 1 to day 4 compared to number of patients screened
- Completion of data. A rate of greater than 80% of randomized participants with complete data set is considered feasible
- Acceptability of subcutaneous lidocaine (lignocaine) or control infusion and study design to participants and carers (sub study)
- Impacts of the intervention relevant to participants and carers (sub-study)
- Time taken to complete study measures at the assessment prior to dose change

Preliminary Toxicity

- Prospectively sought adverse events with the likelihood of relationship to intervention

Pathophysiology

- The median dose at study completion
- The relationship between serum lidocaine (lignocaine) level at steady-state and continuous subcutaneous infusion dose (sub-study)
- Preliminary relationship between serum lidocaine (lignocaine) level and efficacy and toxicity (sub study)

Preliminary Quality of Life and Health Services Utilization

- Completion rate of EQ-5D-5L(generic)
- Arithmetic mean of the 7 items assessing interference on the BPI-SF on day 4 compared with baseline; this mean can be used if more than 50%, or 4 of 7, of the total items have been completed on a given administration
- Total RUG-ADL score on day 4 compared to baseline
- Lidocaine (lignocaine) and analgesic medication costs
- Management of adverse effects, e.g., investigations, additional clinician review, medications
- Inpatient stays (length of stay, AR-DRG), excluding pharmacy costs

Preliminary Efficacy

Exploratory efficacy outcomes will include the following.

- The proportion of participants who have an improvement from baseline to day 4 in:
  - Average pain of 1 point or more on the BPI-SF
  - Worst pain of 2 point or more on the BPI-SF (moderate clinically important difference)
  - Average pain of 2 point or more on the BPI-SF
  - Worst pain of 4 points or more on the BPI-SF (major clinically important difference)
  - Average pain of 4 points or more on the BPI-SF
  - Worst pain to be reduced to ≤3 on the BPI-SF
  - Average pain to be reduced to ≤3 on the BPI-SF
  - Arithmetic mean of worst, least, average and now pain of 1 point or more on the BPI-SF
  - Number of breakthrough pain medications used
  - Burning (superficial) spontaneous pain of 1 point or more on the Neuropathic pain symptom inventory (NPSI)
  - Pressing (deep) spontaneous pain of 1 point or more on the NPSI
  - Paroxysmal pain of 1 point or more on the NPSI
  - Evoked pain of 1 point or more on the NPSI
  - Paresthesia/Dysesthesia of 1 point or more on the NPSI
- Global impression of change measured on a 7-point scale
- Mean change in worst pain on BPI-SF
- Mean change in average pain on BPI-SF
- Proportion of participants who achieve their personalized pain goal
- Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 OR those who have unchanged pain but a reduction in number of breakthrough medications used in the last 24 hours
- Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 AND breakthrough medication use which is unchanged or reduced in the last 24 hours
- Cumulative responders for all changes in worst pain score on BPI-SF on day 4
- Cumulative responders for the proportion of participants who have a reduction in worst pain score of 1 point or more on day 2, 3 and 4
- The proportion of responders, defined by a 1-point reduction in worst pain at day 4, who have a continued response at day 9, 15 and 29 will be calculated for each group.

Subgroup analysis will be performed to evaluate the following for potential as biomarkers of response to lignocaine

1. patients who have never had an adjuvant therapy vs. patients who have not been on the maximal doses listed in appendix.
2. patients who are on minimal, moderate and large doses of morphine (<60, 60−200, >200 mg/day)
3. patients who have severe pain (≥7/10) and moderate pain (4−6/10)
4. patients with allodynia

Supplementary Table 3
Key Outcome Measures

Instrument	Details
Eligibility and Demographic Measures	
Leeds assessment of neuropathic symptoms and signs (LANSS)	Seven item scale including sensory description and examination. Score of 12 or greater has 85% sensitivity that neuropathic mechanisms likely contribute to the patient's pain[29]
Charlson Comorbidity Index (CCI)	Score composed of major comorbidities weighted to reflect risk of death[33]
Nonpharmacological management	Use of patient education, pain diary, physiotherapist, occupational therapist, psychologist, music therapist or other complementary therapy to improve pain management collected from medical record or participant recollection. Recommended by guidelines[34]
Feasibility Measures	
Completion rate	An audit tool based on the study assessments and schedule[13] was developed
Efficacy Measures	
Brief Pain Inventory−Short Form (BPI-SF)	Validated 9-item tool based primarily on 0−10 numeric rating scale assessing pain intensity and interference in the previous 24 hours. Worst and average pain were chosen as key outcome measures of preliminary efficacy
Neuropathic Pain Symptom Inventory (NPSI)	Validated 12-item questionnaire to assess neuropathic pain which may detect treatment effect.[35,36] Ten items are assessed on a 0−10 numeric rating scale and combined to give a score out of 10 covering each of the domains of superficial and deep spontaneous pain, paroxysmal pain, evoked pain and paresthesia/dysesthesia. The sum of the ten items gives a total intensity score out of 100. Items cover the domains of superficial and deep spontaneous pain, paroxysmal pain, evoked pain and paresthesia/dysesthesia.
Health Outcome and Resource Use Measures	
EQ-5D-5L	Validated tool measuring 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) of health-related quality of life with relevant population norms[37–39] The EQ-5D-5L responses were used to determine utility values[27] which can be used to calculate quality-adjusted life years (QALYs) in a cost-utility analysis.
Global impression of change	Seven-point scale regarding participant perception of change in overall status since study commencement; graded from "very much worse" to "very much improved"
Australia-modified Karnofsky Performance Status (AKPS)	Validated scale measuring performance status from 100 (normal) to 0 (dead)[40]
Resource Utilisation Group Activities Daily Living (RUG-ADL)	Four-item scale measuring patient motor function for activities of daily living including bed mobility, toileting, transfers and eating,[41] of most value when AKPS is less than 60[42]
Australian Refined Diagnosis Related Group (AR-DRG)	Groups inpatient stays into clinically meaningful categories of complexity that consume comparable resources.[43] The daily admission cost was estimated using Australian Refined Diagnosis-Related Groups (AR-DRG) codes.
Toxicity Measures	
Adverse effects	Documented using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 terminology with indication of severity, likely causality, and action taken. Vital signs, electrocardiogram (ECG), and structured toxicity assessment will aid this. These will be measured in a full assessment daily. An additional focused toxicity screen will occur 3 hours after dose changes to improve safety.

Supplementary Table 4
Prescreening Failure Reasons

Total screen failure 107	
23	Worst pain score not 4 or greater on 11-point rating scale
18	Inability to complete study assessments
15	insufficient analgesic pretreatment
8	Pain not related to cancer or its treatment
7	Does not want or not appropriate for admission
7	Prescribed beta blocker
5	Pain does not have neuropathic features
4	Liver failure or metastases
3	Abnormal vital signs
3	Patient or clinician did not want control group
3	Patient already on lidocaine infusion
3	Distress or anxiety
2	Cancer (solid or hematologic)
2	History of seizure
1	Patient declined - other
1	Limited access due to isolation
1	Taking mexiletine
1	On another clinical trial

Supplementary Table 5

All Preliminary Efficacy Outcomes, Randomized Set (Categorical Values)

Outcome	Randomized: Lidocaine	Randomized: Placebo	*P*-value
From baseline to cessation	**Participants with improvement**		
Number (%) of participants with improvement of	**N=10**[+]	**N=7**[+]	
Worst pain of ≥1 point on BPI-SF	6 (60%)	4 (57%)	0.91
Worst pain of ≥2 point on BPI-SF	4 (40%)	4 (57%)	0.49
Worst pain of ≥4 point on BPI-SF	0 (0%)	3 (43%)	0.023
Worst pain reduced to ≤3 on BPI-SF	1 (10%)	3 (43%)	0.12
Average pain of ≥1 point on BPI-SF	3 (30%)	5 (71%)	0.092
Average pain of ≥2 point on BPI-SF	2 (20%)	4 (57%)	0.11
Average pain of ≥4 point on BPI-SF	0 (0%)	2 (29%)	0.072
Average pain reduced to ≤3 on BPI-SF	0 (0%)	4 (57%)	0.006
Number of breakthrough pain medications used	3 (30%)	2 (29%)	0.95
Proportion of participants who achieve their personalized pain goal	1 (10%)	3 (43%)	0.12
Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 OR those who have unchanged pain but a reduction in number of breakthrough medications used in the last 24 hours	6 (60%)	5 (71%)	0.63
Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 AND breakthrough medication use which is unchanged or reduced in the last 24 hours	3 (30%)	1 (14%)	0.45
Number of participants with improvement of ≥1 point:	**N=9**[+]	**N=7**[+]	
Mean of worst, least, average and now pain of ≥1 point on BPI-SF	5 (56%)	5 (71%)	0.52
Burning (superficial) spontaneous pain on NPSI (%)	3 (33%)	4 (57%)	0.34
Pressing (deep) spontaneous pain on NPSI (%)	2 (22%)	4 (57%)	0.15
Paroxysmal pain on NPSI (%)	4 (44%)	5 (71%)	0.28
Evoked pain on NPSI (%)	2 (22%)	4 (57%)	0.15
Paresthesia/Dysesthesia on NPSI (%)	3 (33%)	4 (57%)	0.34
At cessation:			
Global impression of change (number)			0.31
very much improved	1 (11%)	0 (0%)	
much improved	1 (11%)	4 (57%)	
minimally improved	2 (22%)	2 (29%)	
no change	2 (22%)	1 (14%)	
minimally worse	0 (0%)	0 (0%)	
much worse	1 (11%)	0 (0%)	
very much worse	2 (22%)	0 (0%)	
Mean pain of ≥1 point on BPI-SF	5 (56%)	5 (71%)	0.52
Number of participants with improvement from baseline to follow-up for:	**Number of responses varied**		
Worst pain of ≥1 point on BPI-SF at day 8	1 (33%)	1 (20%)	0.67
Worst pain of ≥1 point on BPI-SF at day 15	0 (0%)	2 (40%)	0.44
Worst pain of ≥1 point on BPI-SF at day 29	0 (0%)	1 (33%)	0.5

[+] Number of participants randomised to lidocaine/placebo and had complete relevant data. One participant (lidocaine) had incomplete patient reported outcome data at day 4.

Supplementary Table 6
All preliminary Efficacy Outcomes, Per Protocol Set

Outcome	Allocated: Lidocaine	Allocated: Placebo	*P*-value
From baseline to cessation	**Participants with improvement**		
Number (%) of participants with improvement of:	N=**9**[#]	**N=6**[#]	
Worst pain of ≥1 point on BPI-SF	6 (67%)	4 (67%)	>0.099
Worst pain of ≥2 point on BPI-SF	4 (44%)	4 (67%)	0.4
Worst pain of ≥4 point on BPI-SF	0 (0%)	3 (50%)	.018
Worst pain reduced to ≤3 on BPI-SF	1 (11%)	3 (50%)	0.095
Average pain of ≥1 point on BPI-SF	4 (44%)	4 (67%)	0.4
Average pain of ≥2 point on BPI-SF	3 (33%)	3 (50%)	0.52
Average pain of ≥4 point on BPI-SF	0 (0%)	2 (33%)	0.063
Average pain reduced to ≤3 on BPI-SF	0 (0%)	4 (67%)	0.004
Number of breakthrough pain medications used	3 (33%)	2 (33%)	>0.99
Proportion of participants who achieve their personalized pain goal	1 (11%)	3 (50%)	0.095
Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 OR those who have unchanged pain but a reduction in number of breakthrough medications used in the last 24 hours	6 (67%)	5 (83%)	0.47
Proportion of responders, defined as those who have at least a 1-point reduction in pain on day 4 AND breakthrough medication use which is unchanged or reduced in the last 24 hours	3 (33%)	1 (17%)	0.47
Number of participants with improvement of ≥1 point:	**N=8**[#]	**N=6**[#]	
Mean of worst, least, average and now pain of ≥1 point on BPI-SF	6 (75%)	4 (67%)	0.73
Burning (superficial) spontaneous pain on NPSI (%)	3 (38%)	3 (50%)	0.64
Pressing (deep) spontaneous pain on NPSI (%)	3 (38%)	3 (50%)	0.64
Paroxysmal pain on NPSI (%)	4 (50%)	4 (67%)	0.53
Evoked pain on NPSI (%)	3 (38%)	3 (50%)	0.64
Paresthesia/Dysesthesia on NPSI (%)	3 (38%)	3 (50%)	0.64
At cessation:			
Global impression of change (number)	**N=8**[#]	**N=6**[#]	0.26
very much improved	1 (12%)	0 (0%)	
much improved	1 (12%)	4 (67%)	
minimally improved	2 (25%)	1 (17%)	
no change	2 (25%)	1 (17%)	
minimally worse	0 (0%)	0 (0%)	
much worse	0 (0%)	0 (0%)	
very much worse	2 (25%)	0 (0%)	
Number of participants with improvement from baseline to follow-up for:	**Number of responses varied**		
Worst pain of ≥1 point on BPI-SF at day 8	1 (33%)	1 (20%)	0.67
Worst pain of ≥1 point on BPI-SF at day 15	0 (0%)	2 (40%)	0.44
Worst pain of ≥1 point on BPI-SF at day 29	0 (0%)	1 (33%)	0.5

[#]Number of participants allocated to lidocaine/placebo who completed 72 hours of study treatment and had complete relevant data. One participant (lidocaine) had incomplete patient reported outcome data at day 4.

Supplementary Table 7
All Adverse Events From Baseline to Day 29

	All Events (n=63)		Grade 3 or worse (n=12)		SAE (n=5)	
System Organ Class/ Preferred Term	Allocated to Lidocaine	Allocated to Placebo	Allocated to Lidocaine	Allocated to Placebo	Allocated to Lidocaine	Allocated to Placebo
Total number of adverse events	43	20	7	5	3	2
Nervous system disorders						
Ataxia	3 (27%)	0	0	0	0	0
Depressed level of consciousness	2 (18%)	0	1 (9%)	0	0	0
Dizziness	3 (27%)	0	0	0	0	0
Headache	0	2 (33%)	0	0	0	0
Lethargy	1 (9%)	0	0	0	0	0
Movement involuntary	0	1 (17%)	0	0	0	0
Paresthesia	2 (18%)	0	0	0	0	0
Somnolence	3 (27%)	0	0	0	0	0
Tremor	5 (45%)	0	0	0	0	0
General disorders and administration site conditions						
Fatigue	3 (27%)	0	2 (18%)	0	0	0
Gait Disturbance	1 (9%)	0	0	0	0	0
Hyperhidrosis	1 (9%)	0	0	0	0	0
Injection Site Reaction	0	1 (17%)	0	0	0	0
Respiratory disorders						
Dyspnea	2 (18%)	0	0	0	0	0
Sore Throat	1 (9%)	0	0	0	0	0
Eye Disorders						
Blurred Vision	2 (18%)	0	0	0	0	0
Cardiac Disorders						
Palpitations	1 (9%)	0	0	0	0	0
Sinus Bradycardia	1 (9%)	0	0	0	0	0
Sinus Tachycardia	1 (9%)	0	0	0	0	0
Psychiatric Disorders						
Agitation	1 (9%)	1 (17%)	1 (9%)	0	0	0
Anxiety	1 (9%)	1 (17%)	0	0	0	0
Confusion	1 (9%)	1 (17%)	0	0	0	1 (17%)
Delirium	0	1 (17%)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Neoplasms	3 (27%)		3 (27%)	1 (17%)	3 (27%)	1 (17%)
Vascular Disorders						
Hypertension	1 (9%)	2 (33%)	0	2 (33%)	0	0
Hypotension	1 (9%)	0	0	0	0	0
Gastrointestinal Disorders						
Abdominal Pain	0	2 (33%)	0	1 (17%)	0	0
Constipation	1 (9%)	0	0	0	0	0
Nausea	0	1 (17%)	0	0	0	0
Musculoskeletal Disorders						
Back Pain	1 (9%)	0	0	0	0	0
Myalgia	0	1 (17%)	0	0	0	0
Arthralgia	0	2 (33%)	0	0	0	0
Ear and labyrinth disorders						
Tinnitus	1 (9%)	0	0	0	0	0
Infection and Infestations						
Fever	0	1 (17%)	0	0	0	0
Sepsis	0	1 (17%)	0	1 (17%)	0	0
Hepatobiliary Disorders						
Gallbladder pain	0	1 (17%)	0	0	0	0