Original Article

A Phase II Pilot Study to Evaluate Use of Intravenous Lidocaine for Opioid-Refractory Pain in Cancer Patients

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Abstract

Opioid-refractory pain is distressing because it is notoriously difficult to treat. Relief from adjuvant therapies often occurs after a lag time. Retrospective evidence points to a role for intravenous (IV) lidocaine in this setting for pain relief. This study was planned as a randomized, double-blind, placebo-controlled, crossover study in which eligible patients received both lidocaine and placebo infusions separated by two weeks. Primary endpoints were magnitude and duration of pain relief. Fifty patients were included in the study. Pain relief was significantly better ($P < 0.001$) and more patients reported a decrease in analgesic requirements ($P = 0.0012$) after lidocaine infusion than after placebo. Onset of analgesia was noted at a mean of 40 ± 16.28 minutes after initiation of infusion of IV lidocaine. Mean duration of this analgesia, 9.34 ± 2.58 days after the single infusion, was significantly longer than that for placebo ($P < 0.01$). Side effects observed were tinnitus, perioral numbness, sedation, light-headedness, and headache. All side effects were self-limited and did not require any intervention except termination of lidocaine infusion in one case. These data demonstrate that a single IV infusion of lidocaine provided a significantly greater magnitude and duration of pain relief than placebo infusion in opioid-refractory patients with cancer pain. Side effects were tolerable. It is thus a promising modality worth investigating further to establish guidelines for its use in cancer patients with opioid-refractory pain. J Pain Symptom Manage 2009;37:85–93.

Key Words

Intravenous, lidocaine, cancer pain, opioid refractory, side effect, durability of response, duration of response, single infusion

Introduction

Opioid-refractory pain is distressing because it is notoriously difficult to treat. Some patients, particularly those with neuropathic pain, may benefit from tricyclic antidepressants, anticonvulsants, or antiarrhythmics. However, relief usually requires a few weeks, during which the dose has to be titrated. Analgesic interventions with a more rapid onset would be valuable.

Evidence for an analgesic effect of intravenous (IV) sodium channel blockers, such as lidocaine, in chronic non-neuropathic pain is equivocal. However, some authors have posited that parenteral lidocaine may be rapidly

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effective for opioid-refractory pain and have called for a randomized controlled trial to confirm uncontrolled observations.[1] This Phase II pilot study was planned to explore the efficacy and potential uses of IV lidocaine for pain relief in opioid-refractory cancer pain.

Patients and Methods

The study was planned as a randomized, double-blind, placebo-controlled, crossover study of IV lidocaine in opioid-refractory cancer pain. Primary endpoints were magnitude of pain relief and the durability of response. The secondary endpoint was the safety profile, with specific reference to acute side effects. Fifty consecutive patients were recruited between November 2005 and May 2007 from a single center after appropriate regulatory approval.

Patients above the age of 18 years suffering from opioid-refractory cancer pain were considered eligible for this study if they had no serious neurological or cardiovascular comorbidity or allergy to lidocaine. In this study, opioid-refractory pain was defined as pain not responding to a maximally tolerated morphine dose. Any patient who required more than four rescue doses of analgesics for pain relief was offered the next appropriate therapy or intervention for pain control, as per the discretion of the treating Pain Relief and Palliative Care (PRPC) specialist. However, patients had to consent to no change in analgesic therapy from 48 hours before and 24 hours after completion of the scheduled infusion for inclusion in the study.

After obtaining written informed consent, eligible patients received infusions of lidocaine and placebo in random order. Infusions were administered double-blind and there were 14 days between the two infusions.

Infusions were planned as equal volumes of lidocaine or saline (placebo). An initial bolus over 20 minutes was followed by delivery of the remaining volume over the next one hour. The dose was 2 mg/kg (bolus) and 2 mg/kg for slow infusion over next one hour (total dose 4 mg/kg).

An evaluation of the patient's pain score using a Numeric Analog Scale (NAS) (scale from 0 to 10, with 0 being no pain and 10 being worst imaginable pain) was done immediately before starting each infusion, immediately after completion of each infusion, and two hours after completion of the infusion. Patients were instructed to report any significant change in pain score at any time it was appreciable.

Patients were carefully monitored during and for two hours after completion of the infusion with continuous three-lead electrocardiograph (ECG), noninvasive blood pressure every 10 minutes, and respiratory rate every 10 minutes. Any adverse effects, such as arrhythmia, blurred vision, headache, malaise, metallic taste, nausea and vomiting, perioral numbness and tingling, sedation, tinnitus, and tremors, were noted.

Patients were instructed to keep a daily score of the baseline pain (worst pain lasting for at least 30 minutes) experienced in the preceding 24 hours for a period of the next 14 days, and a record of the frequency of rescue medications needed. Duration of effective analgesia (pain relief) was defined as the time taken for the pain score to rise by at least 50% of the maximum magnitude of decrease noted at the end of the observation period of two hours after the infusion (e.g., if the pain scores pre- and postinfusion were 10 and 2, respectively, duration of relief was taken as time for pain score to rise to 6). At the end of the study, patients were asked to subjectively report on the efficacy of both infusions.

Randomization was done by presealed envelopes numbered in a random order (using a random number table) opened immediately before infusion by a research coordinator, who prepared the solutions (as per the randomization code) for infusion by a study nurse, thereby ensuring double-blinding. Data were evaluated using statistical software SPSS version 11.0 (SPSS Inc., Chicago, IL), applying the appropriate statistical tools (e.g., paired *t*-test to compare means and Fisher's exact *t*-test).

Results

After initial screening, 88 patients were found to be eligible for this study. Of these, 26 patients refused consent and another 12 opted out of the study after one infusion and hence are not included in the final analysis.

The demographic profile of the 50 patients recruited for this study is shown in Table 1. The distribution of disease by location is

Table 1
Demographic Profile of Patients

Age [yr; mean ± SD (range)]	67.16 ± 16.21 (34–91)
Sex (male/female)	28/22
Duration of symptoms [mo; mean ± SD (range)]	9 ± 6 (1.5–22)
Nature of pain [*n* (%)]	
Mixed	26 (52)
Nociceptive	15 (30)
Neuropathic	9 (18)

depicted in Table 2. Thirty-two patients (64%) were receiving oral morphine (mean dose 72.34 ± 22.84 mg, range 45–120 mg) for their pain, whereas 39 patients (78%) were receiving adjuvant analgesics at the time of inclusion in the study. Patients who were not receiving morphine had had an unsuccessful opioid trial for pain relief before inclusion in the study.

The mean pain score recorded before each infusion was similar across the entire cohort (lidocaine: 8.48 ± 1.05, range 7–10; placebo: 8.68 ± 0.93, range 7–10), with no significant difference observed before starting either infusion ($P = 0.34$). The pain scores of individual patients are depicted in Fig. 1.

Mean magnitude of decrease in pain score after lidocaine was 6.34 ± 1.73 (range 3–10), this being significantly more compared to mean decrease of 2.30 ± 2.40 (range −2 to 8) with placebo ($P < 0.0001$). Magnitude of change in pain scores for individual patients is depicted in Fig. 2.

In terms of percentage reduction (from baseline before infusion), after lidocaine infusion, the mean percent pain reduction was 74.48% ± 17.16% (range 43%–100%), compared to 25.57% ± 27.82% (range −29% to 100%) after placebo—a highly significant difference in magnitude of response ($P < 0.001$). Fig. 3 depicts the number of patients in increments of 10% relief and shows that the quantum of response was higher after lidocaine infusion. Statistically, a highly significant difference was observed in the number of patients reporting more than 50% reduction in their pain scores from baseline after lidocaine infusion compared to placebo infusion (41 [82%] vs. 8 [16%], respectively; $P = 0.0001$) (Fig. 4). Comparative graphic representation of effects of lidocaine and placebo are shown in Fig. 5.

Table 2
Distribution of Disease by Location

Location	*n* (%)
Upper extremity	7 (14)
Lower extremity	9 (18)
Head and neck region	14 (28)
Chest	4 (8)
Abdominal	9 (18)
Retroperitoneal	7 (14)

Mean time to observe the onset of maximum analgesic effect after initiating the infusion was much earlier (40 ± 16.28 minutes, range 10–70 minutes) after lidocaine, whereas that with placebo was delayed (74.80 ± 33.39 minutes, range 40–120 minutes); the difference was very significant ($P < 0.001$).

Mean duration of pain relief after lidocaine was 9.34 ± 2.58 days (range 4–12 days), compared to a mean duration of 3.82 ± 1.87 days (range 0–8 days) of pain relief with placebo. The difference is significant in favor of lidocaine ($P < 0.0001$).

Thus, pain relief with lidocaine infusion was not only of earlier onset, but also of longer duration compared to placebo. Also, the quality of pain relief with lidocaine was much better. This is borne out by the difference in mean pain score recorded during the 14-day observation period after each infusion (lidocaine: 1.44 ± 1.43, range 0–5; placebo: 5.20 ± 2.25, range 1–9; $P < 0.001$).

The subjective change in analgesic requirement over the period of 14 days after each infusion is shown in Table 3. Significantly more patients reported a subjective decrease in analgesic requirements after lidocaine infusion than placebo (32 [64%] vs. 15 [30%] patients, respectively; $P = 0.0012$), indicating the efficacy of lidocaine infusion in providing pain relief. Although more patients reported a subjective increase in analgesia requirements after placebo infusion compared to lidocaine infusion (12 [24%] vs. 6 [12%] patients, respectively), this difference was not significant statistically ($P = 0.19$).

Frequency of rescue medications used after lidocaine infusion was significantly lower compared to placebo (1.45 ± 0.20 per day after lidocaine vs. 1.76 ± 0.25 per day after placebo; range 0–6 per day for both; $P = 0.01$). Fourteen patients (four after lidocaine infusion and 10 after placebo infusion) requested consultation with the treating PRPC specialist to avail themselves of the option of next appropriate therapy or intervention, as per the study protocol. This difference, in number of patients requesting

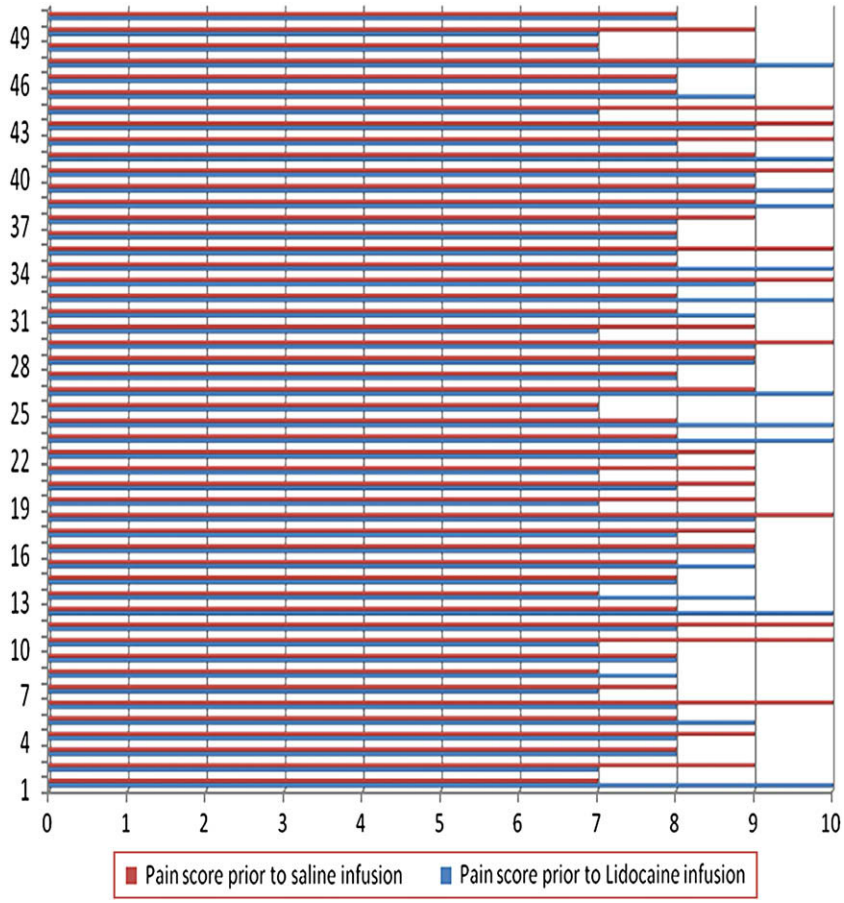

Fig. 1. Chart depicting individual NAS pain score before each infusion (lidocaine and saline).

other pain relief treatments after the two infusions, was not statistically significant ($P = 0.14$).

Mean decrease in the heart rate observed during the infusion and in peri-infusion period (up to two hours after the infusion) was significantly more ($P < 0.0001$) in the case of lidocaine (38.64 ± 12.56, range 14–58) compared to placebo (7.28 ± 8.98, range −6 to 28). The mean time to observe the maximum change in heart rate was significantly ($P < 0.001$) earlier in patients receiving lidocaine infusion (19.8 ± 10.97 minutes, range 10–40 minutes) compared to placebo (32.0 ± 16.28 minutes, range 10–60 minutes). However, no patient experienced arrhythmia (any abnormality of the heart rhythm from baseline) or bradycardia (heart rate < 50) at any point during either infusion or in the follow-up observation period (changes in PR, QRS, QT intervals were not specifically captured or analyzed to evaluate for arrhythmia). Mean of minimum heart rate observed during lidocaine infusion was 84.28 ± 10.54 (range 70–110), whereas that during placebo infusion was 108.84 ± 10.50 (range 92–128). Also, no significant change in blood pressure (systolic or diastolic) during or after the infusions was noted.

The side effects that were observed during infusion and in the peri-infusion period were perioral numbness, sedation, light-headedness, tinnitus, and headache. The distribution of side effects observed during the infusions is mentioned in Table 4.

Twenty-six (52%) patients experienced at least one side effect after infusion of lidocaine, whereas 18 (36%) experienced at least one side effect after infusion of placebo. This difference is not statistically significant ($P < 0.2$). However, significantly more patients experienced two or more side effects after lidocaine infusion (10 and two patients experienced two and three side effects, respectively), compared to after placebo infusion (two patients and none, respectively) ($P = 0.006$). The time to develop

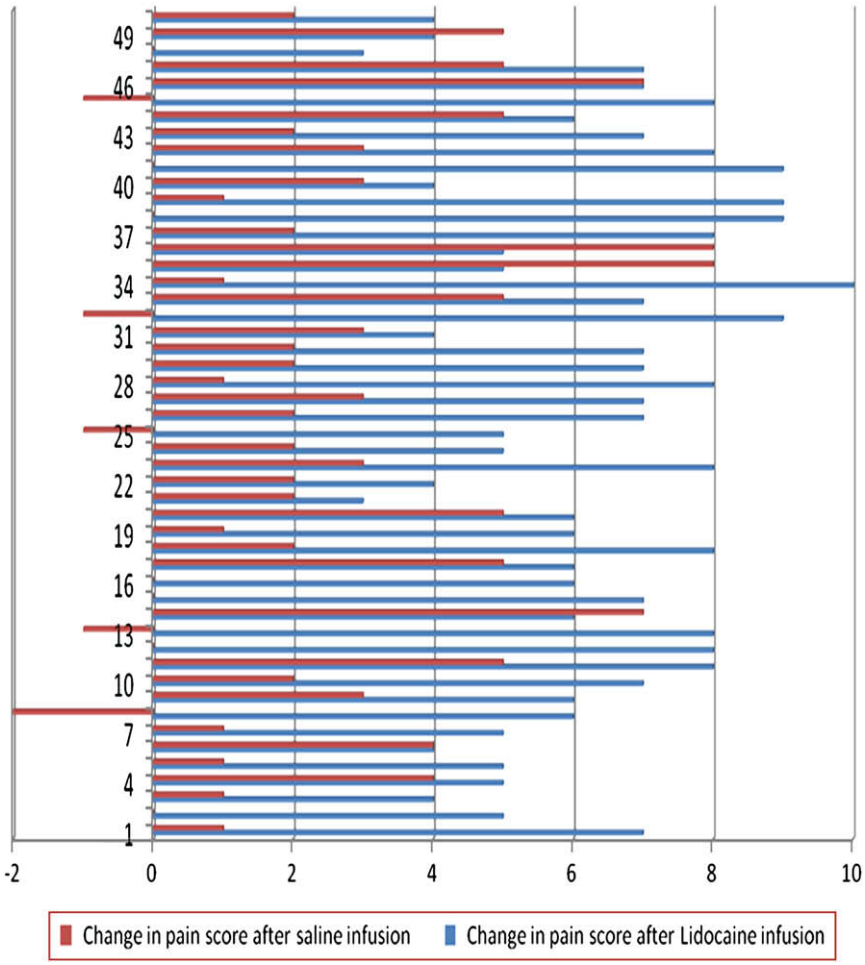

Fig. 2. Chart depicting the magnitude of change in pain scores for individual patients after each infusion (lidocaine and saline).

side effects was earlier after lidocaine infusion (14.5 ± 6.77 minutes, range 5–30 minutes) compared to placebo infusion (35.89 ± 11.78 minutes, range 12–62 minutes); the difference was statistically significant ($P = 0.005$).

Only one patient required termination of infusion due to side effects. This patient required termination of lidocaine infusion due to severe tinnitus, which started after about 30 minutes of infusion and required termination by 44 minutes. This patient also experienced sedation and perioral numbness. Side effects were self-limiting once infusion was stopped and gradually subsided in three hours after cessation of the infusion.

More patients reported the lidocaine infusion as the better infusion. Thirty (60%) patients rated lidocaine as better compared to 14 (28%) who rated placebo as better ($P = 0.0023$). Six (12%) patients found both infusions equal in efficacy. It is interesting to note that irrespective of the subjective choice of better infusion, percentage of pain relief (compared to baseline before infusion) was consistently higher after lidocaine infusion compared to placebo infusion, although the difference is much more in patients who found lidocaine to be superior to placebo (Fig. 6).

Discussion

Pain is not a discrete sensory experience that is switched on by a defined set of "stimuli" acting on a specific "pathway" to elicit an invariant sensation. Instead, pain is a diverse set of complex perceptual events that are characterized by their unpleasant or distressing

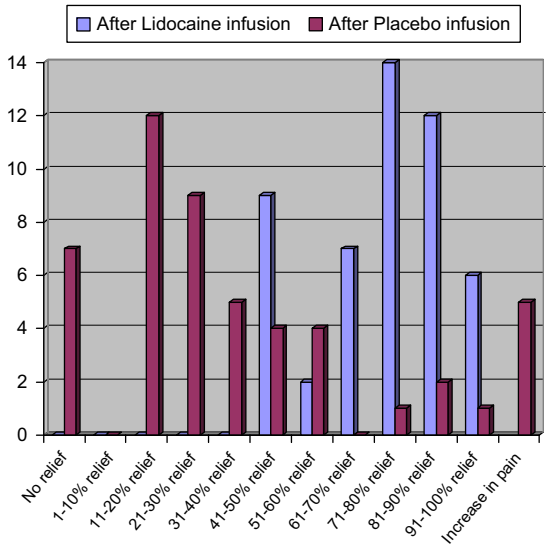

Fig. 3. Chart depicting percent response (groups of 10% increments) after each infusion.

nature. Potent opioids are excellent painkillers but their use is hampered by side effects such as nausea, vomiting, bowel dysfunction, urinary retention, pruritus, and sedation. When pain becomes chronic, particularly when it results from progressive disease such as malignancy, it may become unresponsive even to opioids. In such situations, the physician faces a difficult scenario—how to relieve pain with minimum side effects, and more importantly, how to give immediate relief until additional medications or interventions take effect.

The first description of the use of an IV local anesthetic as an analgesic appeared more than 60 years ago.[2,3] Many reports since then have confirmed this effect and yet the use of IV local anesthetics has not become a widespread practice.

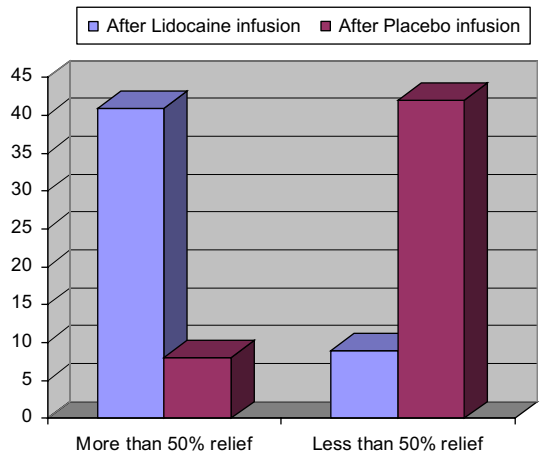

Fig. 4. Chart depicting number of patients showing response (>50% pain relief) after each infusion.

There is a dearth of randomized trials exploring the use of IV lidocaine in analgesia, although retrospective reviews and a number of case reports exist, both supporting[1,4–9] and discounting[10,11] its use in such a setting. These studies have noted a variable duration of effect lasting from a few hours to as long as a few weeks after a single infusion. A long duration of analgesic effect, if confirmed, may have a potential benefit in terms of not only less frequent doses, but also a more favorable side effect profile. Pertinent to its use as an adjuvant analgesic, it is important to note that, unlike regular analgesics that need to be given "by the clock" to achieve adequate analgesia, lidocaine is administered over a relatively short period of time and yet the potential relief lasts significantly beyond both the period of administration and its plasma half-life.[5,7–9]

We found a mean duration of pain relief of 9.34 days after single infusion in this study, which is much beyond the period of infusion (80 minutes in our study) or the pharmacological half-life of the drug (60–90 minutes) in plasma. A possible explanation of this prolonged effect may lie in the observation by Tsai et al.[12] They observed that in healthy humans, a single IV bolus injection of lidocaine resulted in a sustained and constant concentration lasting for more than one hour in

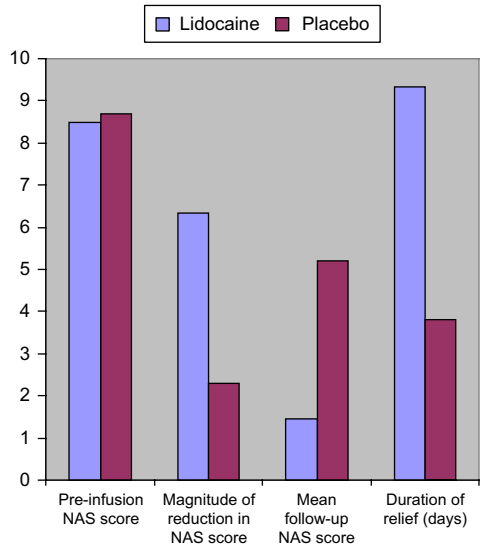

Fig. 5. Comparative chart for effect of lidocaine and placebo.

the cerebrospinal fluid, whereas the plasma levels showed a faster decay.

A number of limited studies (Phase I experimental studies) have suggested that patients with pain generated from dysfunctional dorsal roots, dorsal root ganglia, or peripheral nerves are much more likely to report pain relief from IV lidocaine than patients with central nervous system injury.[13–16] The doses used ranged from 2 to 5 mg/kg/hr for 1 to 2 hours, which are associated with plasma levels of 1 to 3 μg/mL (the lower level of the antiarrhythmic range). Few side effects were encountered at this dose level. A number of other authors have also attested to the safety of lidocaine infusion.[1,4,7–9,13–18]

Attal et al.[14] reported a 68% incidence of side effects after lidocaine infusion (5 mg/kg over 30 minutes), the most common being lightheadedness and drowsiness. Although the incidence was high, the severity of side effects was mostly mild to moderate. Similarly, Thomas et al.[1] reported a 30% incidence of mild to moderate side effects in their review. Drowsiness was again the most common side effect observed and the authors concluded that lidocaine was reasonably well tolerated. Common consensus in this regard is that high dose rate of infusion and use of rapid bolus doses are associated with high incidence of side effects, which are usually mild to moderate in severity and subside soon after cessation of the infusion without need for any specific treatment or intervention.

Table 3
Subjective Requirement of Analgesics After Infusion of Lidocaine or Placebo

Postinfusion Analgesic Requirement	After Lidocaine Infusion *n* (%)	After Placebo Infusion *n* (%)	*P*
Decreased	32 (64)	15 (30)	**0.0012**
Increased	6 (12)	12 (24)	0.19
No change	12 (24)	23 (46)	**0.0353**

Bold numbers represent significant values of P ($P < 0.05$).

Table 4
Side Effects Observed During Infusion of Lidocaine or Placebo

Side Effects	During Lidocaine Infusion *n* (%)	During Placebo Infusion *n* (%)	*P*
Sedation	10 (20)	13 (26)	0.6353
Perioral numbness	7 (14)	0 (0)	**0.0125**
Lightheadedness	6 (12)	3 (6)	0.4870
Tinnitus	8 (16)	0 (0)	**0.0058**
Headache	9 (18)	4 (8)	0.2336
Any side effect	26 (52)	18 (36)	<0.20

Bold numbers represent significant values of P ($P < 0.05$).

In our study, we found that a single infusion of lidocaine was reasonably well tolerated, efficient, and rapidly effective. Although 52% of patients (26 out of 50) experienced side effects in our study, this incidence itself is not significantly different from the placebo group, which had a 36% (18 of 50) incidence of side effects ($P < 0.2$). Twenty percent of patients (10 of 50) experienced sedation with lidocaine infusion, making it the most common side effect observed. Other side effects were noted with much less frequency (Table 4). Tinnitus and perioral numbness were two side effects that we observed with lidocaine alone. The incidence of other side effects was not significantly different from the placebo group.

We observed a decrease in heart rate after lidocaine infusion, which was significantly higher than in placebo group ($P < 0.001$). However, none of the patients experienced bradycardia (defined as heart rate of <50/min) at any point during or after infusion (minimum heart rate recorded during the entire study 70/min).

There are a number of controversies regarding the systemic use of lidocaine in pain management, including mechanism of such action, effective dose range, specific symptoms relieved and thus indications, duration, and endpoint of such use. One interesting observation in our study was that maximal pain relief was

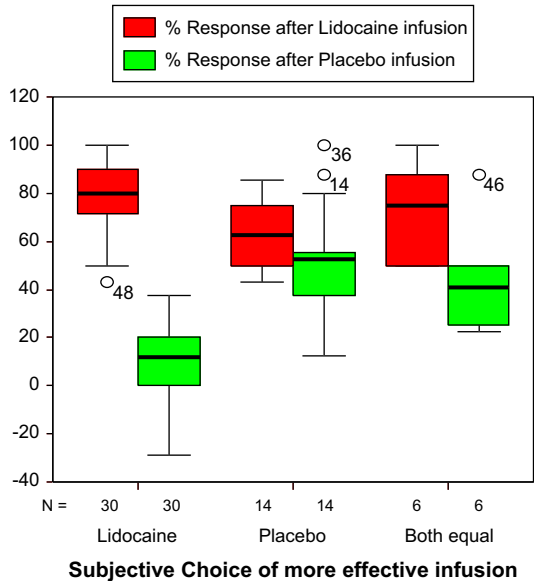

Fig. 6. Chart depicting the percent response seen after each infusion in patients grouped by their subjective choice of better infusion.

invariably observed in the peri-infusion period, possibly indicating some element of power of suggestion being concurrently active.

The exact mechanisms of analgesic action of IV lidocaine remain intensely investigated, hotly debated, and yet poorly understood. Lidocaine can suppress ectopic neural discharges originating from injured primary afferent fibers because of its properties of blocking voltage-gated sodium channels.[19] Bach et al. showed evidence of activation of the endogenous opioid system by systemic lidocaine.[20] These studies point to a mechanism of action different from the peripheral membrane stabilization effect noted pharmacologically.

One of the problems with use of systemic lidocaine as an analgesic adjuvant is that authors of the limited trials available have used various administration schedules with varying total, bolus, and infusion rates. Joad et al.[6] infused 5 mg/kg of lidocaine over 60 minutes; Kastrup et al.[21] used 5 mg/kg in 30 minutes; Galer et al.[13] used two doses, 2 mg/kg and 5 mg/kg, over 40 minutes (and found them both effective but to different degrees); Ferrante et al. administered 500 mg lidocaine over 60 minutes;[22] and Nagaro et al. administered 1.5 mg/kg of lidocaine over one minute.[23]

The therapeutic efficacy of IV lidocaine may be peculiar, being characterized by a precipitous "break in pain" over a narrow dosage and concentration range. Ferrante et al. reported the dose-response relationship of IV lidocaine and noted that the "free concentration of lidocaine had no better correlation with the onset of analgesia or the attainment of analgesia than the serum concentration of lidocaine."[22] They found a large increase in pain relief for concomitant minimal increase in dose (ED_{50} 372.0 mg vs. ED_{90} 416.5 mg) and an abrupt fall in pain score when the serum concentrations rose above 0.62 μg/mL.

The main arguments against IV lidocaine for analgesic use have been two-pronged—one, the associated side effects and two, that it does not produce pain relief in all patients. Quoted studies and our observations, however, point to the safety of IV lidocaine infusion. Most of the side effects observed are postulated to be related more to the speed of infusion. Although the overall incidence of side effects was 52% in our study, all were self-limiting and produced no significant or serious consequences requiring active treatment in any patient. In our study, IV lidocaine infusion produced only a 2% (1 out of 50) incidence of side effects serious enough to warrant any intervention (in this case, termination of infusion). Although it is true that IV lidocaine is not effective in all patients, this would be true for any pain relief modality.

Potential limitations to our study include the progressive nature of disease (causing worsening of existing pain or appearance of new pains), possibility of under-dosing with 4 mg/kg given over 80 minutes (effective dose rate 3.07 mg/kg/hr), inherent physiological variability in response to analgesic adjuvants, and the crossover nature of the study with possibility of carryover effect. Although carryover effect is a theoretical possibility, the baseline pain scores and duration of evaluation were similar before each infusion and the temporal difference between the two infusions is more than the maximum duration of pain relief noted. These make this bias less likely, although our failure to formally analyze this may be a flaw. Another issue is that the study was not powered to study the safety profile of IV lidocaine, as the primary aim was magnitude and duration of pain relief. In our study, serum lidocaine values were not measured; although this may be criticized, it is not essential because this was only a Phase II pilot study.

Conclusions

IV lidocaine seems to be a useful adjunct in achieving significant relief in patients with opioid-refractory pain and the duration of this pain relief, albeit temporary, is much more than the pharmacological half-life of lidocaine in serum. This duration can be effectively used to implement other more established pain control treatment modalities. Additionally, immediate onset of relief from pain relieves the psychological stress on the patient and family and may help the physician develop a better rapport with the patient, allowing for effective psychological counseling and support, both of which are often forgotten but very important components of "pain."

The results of this trial strongly support the use of IV lidocaine for pain relief in opioid-refractory cancer pain. Larger, multicenter, Phase III trials are needed to firmly establish the guidelines for such use and to adequately study the safety profile of IV lidocaine. However, until such guidelines are in place, it is worth considering IV lidocaine as a temporary short-term relief measure in refractory pain.

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