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Differential Effect of Ketamine and Lidocaine on Spontaneous and Mechanical Evoked Pain in Patients with Nerve Injury Pain

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Background: **The mechanisms underlying neuropathic pain are incompletely understood. Targeting specific molecular mechanisms in the pain signaling system may assist in understanding key features in neuropathic pains such as allodynia. This study examined the effect of systemically administered ketamine, an *N*-methyl-D-aspartate receptor antagonist and lidocaine, a sodium channel blocker, on spontaneous pain, brush-evoked pain, and pinprick-evoked pain in patients with nerve injury pain.**

Methods: **Twenty patients participated in two randomized, double-blinded, placebo-controlled, crossover experiments in which they, on four different days, received a 30-minute intravenous infusion of ketamine (0.24 mg/kg), lidocaine (5 mg/kg), or saline. Ongoing pain, pain evoked by brush and repetitive pinprick stimuli, and acetone was measured before, during, and after infusion.**

Results: **Ketamine significantly reduced ongoing pain and evoked pain to brush and pinprick, whereas lidocaine only reduced evoked pain to repetitive pinprick stimuli. In individual patients, there was no correlation between the pain-relieving effect of lidocaine and ketamine on ongoing or mechanically evoked pains.**

Conclusions: ***N*-methyl-D-aspartate receptor-linked systems and sodium channels are involved in generation and maintenance of pain in patients with peripheral nerve injury. It is likely that ongoing pain as well as mechanical hyperalgesia in individual patients is dependent on several separate molecular mechanisms.**

PERIPHERAL nerve injury may give rise to severe and long-lasting types of pain termed *neuropathic* pains, which are often resistant to treatment. Currently, the best available treatments produce moderate to good pain relief in fewer than one third of the patients. A prerequisite for a better treatment is an increased knowledge of the mechanisms underlying neuropathic pain. A mechanism-based approach for classifying and analyzing patients has been proposed as a mode to link treatment strategies to pathophysiological mechanisms responsible for initiation and maintenance of neuropathic pain.[1–3] One way to study such a potential link is to use analgesics with different methods of action targeting a specific mechanism or phenomenon in the same patient or to examine the effect of one analgesic on different types of mechanical hyperalgesia, thermal sensation, and so forth. We recently demonstrated a different effect of gabapentin on brush and pinprick evoked pain in the capsaicin model.[4] Allodynia, that is, pain evoked by a normal nonpainful stimulus, is a classic feature in several peripheral and central neuropathic pain conditions.[5–8] Although the exact mechanisms underlying allodynia are still unclear, an abundant literature indicates that abnormal and increased activity from damaged nerve endings may play a role in generating an increased barrage to second-order neurons located in the dorsal horn of the spinal cord.[9,10] The increased activity from the periphery causes a central sensitization with an array of manifestations, including lowered threshold for exaggerated responses to suprathreshold stimuli, spread of pain beyond the injured site, wind-up–like phenomena, and aftersensations.[3,7,11,12] Experimentally, evidence indicates that increased and abnormal sodium channels in the periphery as well as *N*-methyl-D-aspartate (NMDA) receptor-linked systems are involved in the sensitization processes.[13–17] In experimentally induced sensitization by capsaicin, we previously showed that brush and punctate evoked pain respond differentially to ketamine and lidocaine, indicating that the two types of hyperalgesia do not share a common mechanism.[16] A series of clinical studies have shown that both systemically administered ketamine and lidocaine can reduce ongoing mechanical evoked types of pain in postherpetic neuralgia, diabetic neuropathy, postamputation pain, and nerve injuries.[18–26] However, in individual neuropathic pain patients, it is unknown if a particular phenomenon such as brush evoked pain, pinprick hyperalgesia, or even ongoing pain is mediated by the same or different molecular mechanisms. To address this issue, we selected patients with well-defined peripheral nerve injury and mechanical allodynia and hyperalgesia in the innervation territory of the damaged nerve and exposed them to an intravenous treatment with a sodium channel blocker (lidocaine), a NMDA receptor antagonist (ketamine), or saline and recorded their ongoing and evoked pain before, during, and after each treatment period.

Materials and Methods

Patients

Patients with verified nerve injury pain and mechanical allodynia (pain to light touch) and pinprick hyperalgesia

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(increased pain to painful pinprick stimuli) lasting more than 3 months and attending the neuropathic pain clinic at the Department of Neurology, Aarhus University Hospital, were eligible to enter the study. Severe psychiatric disease, polyneuropathy, diabetes mellitus, symptoms reported to originate from the contralateral side, a history of previous cardiac arrhythmia, or abnormal 12-lead electrocardiograph were exclusion criteria. The patients were allowed to continue present analgesic treatment provided that this was kept stable and unchanged for not less than 1 week before study entry and during the entire study period. Informed written consent was obtained from all participants in the study, which was carried out according to the Helsinki Declaration and approved by the local ethics committee and the Danish National Board of Health, Copenhagen, Denmark.

Psychophysical Measurements

All patients were seen at a screening session at least 1week before the first treatment session. A medical history was obtained and quantitative sensory testing as described below was carried out. Each patient underwent a 12-lead electrocardiograph, and blood pressure was measured. The psychophysical measures were obtained from the most painful allodynic area and in the contralateral mirror image area. Patients unfamiliar with the test procedure were trained in a nonaffected skin area before formal testing was carried out.

Detection and Pain Thresholds. Tactile detection threshold and tactile pain threshold was measured by von Frey hair (Semmes-Weinstein monofilaments, Stoelting, IL; graded from 0.039–4386.40 mN). Pressure pain threshold was determined using a hand-held electronic pressure algometer (Somedic AB, Hörby, Sweden). We used a circular probe with an area of 1 cm^2 with a pressure application of 30 $kPa \cdot s^{-1}$. The threshold was calculated as an average of three measurements. Thermal detection (heat detection threshold, cold detection threshold) and pain threshold (heat pain threshold, cold pain threshold) were measured using the Somedic Thermotest (Somedic AB, Hörby, Sweden). A Peltier thermode with an area of 12.5 cm^2 was applied to the skin. Baseline temperature was set at 30°C, with a thermal change rate of $1°C \cdot s^{-1}$ and an interstimulus interval randomized between 4 and 6 s. The cut-off limit for warmth was 52°C and that for cold was 10°C. Testing was carried out as described previously as the average of five measurements.[6]

Pain Assessment. Spontaneous pain was measured using a visual analog scale (VAS) ranging from 0 to 100 mm (0 = no pain, 100 = unbearable pain). At the screening session, patients were asked about their present pain score and their average pain score during the last week.

Brush-evoked Pain. Brush-evoked pain was elicited by a hand-held painter's brush (foam rubber, 7.0 × 2.5 × 1.5 cm) kept at an angel of 60° when touching the skin. The brush was dragged across the skin 10 times at 2.0 Hz. Stimulation time was 20 s. Evoked pain was scored on an electronic VAS for 60 s before, during, and 100 s after (total, 180 seconds) and data were stored on a computer. The maximal pain VAS score (0 = no pain, 100 = unbearable pain) was calculated. Brush-evoked pain was measured at the screening session before, during (20 min), and after each treatment.

Pinprick-evoked Pain. Evoked pain to repetitive pinprick stimuli was created by an electronic home-built microprocessor-controlled solenoid with an attached nylon filament (bending force, 1234 mN). Repetitive stimulation was carried out with a frequency of 2.0 Hz for 60 s or less if pain became intolerable. Pinprick-evoked pain was scored in a similar fashion as brush-evoked pain. Repetitive pinprick stimulation was carried out 2 min after the brush-evoked pain assessment.

Cold Allodynia. An acetone drop was placed on the allodynic skin at the screening session before, during (18 min), and after the treatment. Patients scored pain evoked by the acetone drop on a VAS.

Reaction Time. Reaction time was measured by self-constructed electronic equipment. The investigator and patient pressed a button at the same time. The patient was not able to watch the investigators push the button. When the investigator released the push button (randomly at 5–10 s between each), a sound was heard and light was seen at a display. The patient was asked to release the push button as soon as the sound was heard or the light was seen on a display. Reaction time was calculated as the average of three consecutive measurements.

Study Design and Drug Infusion. Each patient participated in two randomized, double-blinded, placebo-controlled, crossover experiments. The randomization was such that half of the patients started with experiment 1 and the other half with experiment 2, again in a randomized fashion, thus participating in four treatment sessions. Each treatment session was separated by at least 2 days.

Experiment 1: On two separate examination days, patients received, in random order, an intravenous infusion of lidocaine (20 mg/ml lidocaine, Danish Hospital Pharmacies) or saline (9 $mg \cdot ml^{-1}$ NaCl, Danish Hospital Pharmacies) *via* an infusion pump (Ivac 598; Kivex A/S, Hørsholm, Denmark). Lidocaine was diluted in two bags (100 ml) of isotonic saline, and the total dose was 5 $mg \cdot kg^{-1}$ over the course of 30 min. To ensure blinding between the experiment 1 and 2, lidocaine was infused as a continuous infusion of 1.67 $mg \cdot kg^{-1}$ over the course of 10 min followed by one infusion of 3.33 $mg \cdot kg^{-1}$ over the course of 20 min.

Experiment 2: On two separate examination days, patients received, in random order, an intravenous infusion of ketamine hydrochloride (50 $mg \cdot ml^{-1}$; Keta-

lar®, Parke-Davis, Scandinavia AB, Solna, Sweden) or isotonic saline. Ketamine was diluted in two bags of isotonic saline and infused as a bolus infusion of 0.1 $mg \cdot kg^{-1}$ over the course of 10 minutes followed by an infusion of 0.007 $mg \cdot kg^{-1} \cdot min^{-1}$ over the course of 20 min using an infusion pump. A doctor not involved in the study prepared the bags used for infusion.

During both experiment 1 and 2, electrocardiograph and blood pressure was monitored before infusion and during the entire infusion period. Before the infusion, 20 min after the infusion started, and 20 min after the infusion stopped, evoked pain to acetone drop, pain evoked by brush, and that evoked by repetitive pinprick stimuli were measured. Spontaneous pain was measured at time 0, 10, 20, 30, and 40 (t = 0: start of infusion).

A blood sample was obtained 5 min after the infusion stopped to measure the plasma level of lidocaine and ketamine. To determine whether ketamine or lidocaine impaired sensory perception, reaction time was measured before, during, and at the end of infusion.

Assessment of the Plasma Concentration of Lidocaine and Ketamine

Analysis of ketamine and lidocaine content in plasma samples were performed using gas chromatography mass spectrometry provided by Dr. Ulf Bondesson, Department of Chemistry, National Veterinary Institute, Uppsala, Sweden. The quality control samples for Ketamine analyses at 2.3 $ng \cdot ml^{-1}$ and 156 $ng \cdot ml^{-1}$ (n = 5) varied between 2.5% and 8.7%, respectively, with a lower limit of quantification of 1.1 $ng \cdot ml^{-1}$. Lidocaine at 1057 ng·0.5 ml^{-1} (n = 5) varied 6.8%, and the lower limit of quantification was 1.0 $ng \cdot ml^{-1}$.

Side Effects

Patients were informed about possible side effects of lidocaine and ketamine before inclusion in the study. During and after the infusion, patients were asked if they felt any side effects. The character and duration of any side effects were recorded. Reported side effects were graded on a three-point scale as weak, moderate, or severe.

Statistical Analysis

The present study was carried out in two separate two-way crossover studies. Normal distribution of data was analyzed by the Kolmogorov-Smirnov normality test. Results are presented as either median with ranges, 25%, and 75% percentiles, or as mean ± standard deviation. Side-to-side differences in psychophysical measurements were analyzed by two-tailed *t* test (parametric data) or Wilcoxon signed rank test (nonparametric data).

A mean, ongoing VAS score was calculated during the infusion period, and the difference was analyzed by two-tailed *t* test (parametric data). Treatment efficacy on evoked pain between lidocaine and saline and between ketamine and saline were analyzed by two-tailed paired *t* test.

To examine if response to one analgesic could predict the outcome of the other analgesic, linear regression analysis between spontaneous pain response to ketamine and lidocaine was performed, and a similar analysis was performed for mechanically evoked pain. The relationship between plasma concentrations of active drug and treatment effect was examined by linear regression analysis.

To try to predict the treatment response from baseline psychophysical measures, linear regression analysis was used to examine possible relationships between side-to-side differences in quantitative sensory testing and spontaneous pain response and side-to-side differences in quantitative sensory testing and evoked pain to repetitive stimuli (brush or pinprick stimuli).

P values less than 0.05 were considered to be statistically significant.

Results

A total of 20 patients (7 female, 13 male; mean age, 49 yr; range, 29–73 yr) were included in the study. Table 1 shows the characteristics of the patients. All patients had signs of specific nerve injury as indicated in table 1. Figure 1 shows the distribution of pinprick hyperalgesia and allodynia in each patient. Mean spontaneous pain at the screening session was 50 ± 19 (standard deviation). One patient was excluded during the first treatment session because of side effects described as aggressive behavior and hallucinations during the first infusion period. The remaining 19 patients completed the screening session and all four treatment sessions.

Psychophysical Threshold at Screening Session

All patients had allodynia to light touch and pinprick hyperalgesia in the affected skin area. Confirming the presence of neuropathic pain, patients had decreased sensory threshold to tactile and cold stimuli together with hypersensitivity to painful pressure, cold, and heat in the affected skin (table 2).

Effects of Lidocaine and Ketamine

The mean dose of ketamine (± standard deviation) administered was 18.4 ± 3.8 mg (range, 13.2–27.4 mg), and the mean dose of lidocaine was 377 ± 78 mg (range, 275–570 mg).

Spontaneous Pain Relief

There was no difference in mean spontaneous pain score (± standard deviation) before the beginning of each treatment session: ketamine, 50 ± 27; placebo-

Table 1. Summary of Clinical Characteristics of Patients with Nerve Injury Pain

Patient No.	Sex/ Age (yr)	Cause of Pain	Injured Nerves	Pain Duration (mo)	VAS Ongoing Pain (0–100)	VAS Allodynia Pain (0–100)	VAS Pinprick Hyperalgesia (0–100)	Analgesic Treatment before Study
1	M/57	Traumatic nerve injury	Median and ulnar nerves	7	32	68	60	None
2	M/54	Traumatic nerve injury	Sural nerve	>3	73	100	100	Tramadol
3	F/26	After surgery	Spinal dorsal nerve Th6–L2	22	48	72	89	Tramadol, ibuprofen
4	M/52	After surgery	Supraclavicular nerve, axillary nerve, median brachial cutaneous and intercostobrachial nerve	144	52	67	82	Amitriptyline, Gabapentine, acetaminophen, morphine
5	M/53	Traumatic nerve injury	Radial and median nerves	12	27	90	95	None
6	M/64	After surgery	Intercostal nerves T3–T7	>3	50	25	56	None
7	F/29	After surgery	Supraclavicular nerve, intercostal nerves Th2–Th8	>3	62	22	100	Codeine, acetaminophen, Carisoprodole
8	F/44	After surgery	Peroneal nerve	>3	58	80	100	Clonazepam, carbamazepine
9	F/48	After surgery	Peroneal and saphenous nerves	55	72	86	92	Codeine, acetaminophen
10	M/59	Traumatic nerve injury	Peroneal and saphenous nerves	>3	42	42	37	None
11	M/41	Traumatic nerve injury	Median, ulnar, and radial nerve	24	61	96	100	Acetaminophen, ibuprofen
12	M/54	After surgery	Brachial plexus	16	8	51	68	Acetaminophen, codeine, tramadol
13	M/55	Traumatic nerve injury	Ulnar nerve	62	64	71	76	None
14	M/66	After surgery	Femoral nerve	26	45	56	67	None
15	F/73	After surgery	Peroneal nerve	300	15	69	70	Morphine
16	F/44	After surgery	Intercostal nerves Th6–Th10	36	48	31	32	Gabapentin, tramadol
17	M/2	Traumatic nerve injury	Peroneal nerve	>3	40	56	80	Codeine, acetaminophen
18	M/32	Traumatic nerve injury	Ulnar nerve	>3	73	92	100	None
19	M/58	Traumatic nerve injury	Median, ulnar, and radial nerve	>3	53	74	68	Nitrazepam
20	F/39	After surgery	Radial nerve	>3	73	91	Nd	Codeine, acetaminophen

Nd = not done; VAS = visual analog scale.

ketamine: 46 ± 24; lidocaine, 50 ± 25; placebo-lidocaine, 52 ± 24 (not significant).

Mean spontaneous VAS pain score during the infusion period was significantly reduced by ketamine (41 ± 31) compared with saline (51 ± 24; $P < 0.01$, paired *t* test). Mean spontaneous pain decreased 30% in the ketamine group compared with a mean increase in pain in the placebo group of 1% (fig. 2). A treatment responder was defined as an individual whose mean pain rating decreased by at least 33% during the infusion period compared with baseline.[27] In the ketamine group, 8 of 19 patients (42%) were responders, whereas only 1 patient (5%) in the placebo group had such an effect.

There was no difference between mean spontaneous pain VAS score by lidocaine infusion (45 ± 29) compared with mean spontaneous pain during saline treatment (49 ± 25; not significant). In the lidocaine group, 4 of 19 patients (21%) were responders, whereas there were no responders in the placebo group. Mean spontaneous pain decrease in the lidocaine group was 13%, whereas pain increased with 8% in the placebo group (fig. 2).

To determine whether lidocaine and ketamine responses were linked to a sensitization of peripheral nociceptors, we examined possible relationships between side-to-side differences in warmth, heat, cold sensation; cold pain, pressure pain, and tactile stimuli; and spontaneous pain or evoked pain to mechanical stimuli. There was no relationship between any of the side-to-side differences of psychophysical measures at the screening session (heat detection threshold, heat pain threshold, cold detection threshold, cold pain threshold, tactile detection threshold, tactile pain threshold, and pressure pain threshold) and the effect of lidocaine or ketamine on spontaneous pain, evoked pain to brush, and evoked pain to repetitive pinprick stimuli (data not shown).

Brush-evoked Pain

Maximum evoked pain score (± standard deviation) by repetitive brush was reduced significantly by ketamine

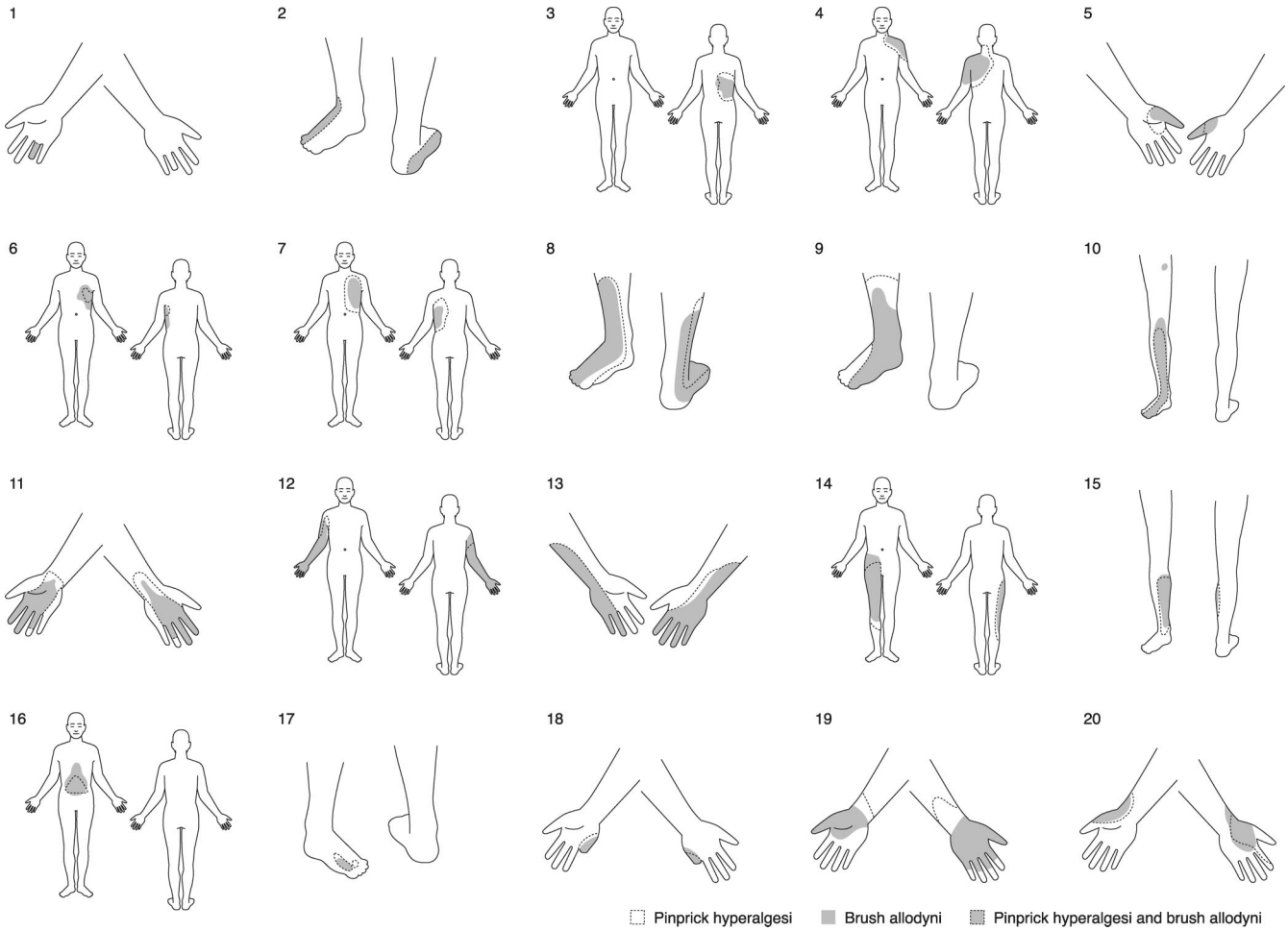

Fig. 1. Sensory characteristics in each individual show the distribution of brush allodynia and pinprick hyperalgesia.

(50 ± 32) compared with saline (64 ± 26; $P < 0.05$, paired t test; n = 19). In contrast, there was no effect of lidocaine infusion on evoked pain score (56 ± 30) compared with saline infusion (63 ± 26; fig. 3).

Pain Evoked by Repetitive Pinprick Stimuli

Pain was evoked in 17 of 19 of patients who fulfilled the experiments. Two of the 19 patients declined to have pain evoked by repetitive pinprick stimuli during treatment sessions because pain evoked by repetitive pinprick stimuli at the screening session was unbearable. The maximum pain score (± standard deviation) evoked

Table 2. Side-to-side Difference of Thermal, Pressure, and Tactile Sensation

	Affected	Nonaffected	*P* Value
HDT (°C)	36.6 ± 5.2	34.4 ± 2.2	NS
HPT (°C)	42.3 ± 4.4*	44.8 ± 4.0	<0.01
CDT (°C)	27.5 ± 2.4*	28.6 ± 0.5	<0.05
CPT (°C)	19.6 ± 7.0*	12.3 ± 4.0	<0.01
PPT (kPa)	109 ± 92*	322 ± 144	<0.01
TDT (mN)	4.03 (0.69; 8.07)	1.66 (0.69; 9.43)	NS
TPT (mN)	54.01 (20.04; 140.35)*	1,236.24 (744.95; 2,384.81)	<0.01

* $P < 0.05$.

CDT = cold detection threshold; CPT = cold pain threshold; HDT = heat detection threshold; HPT = heat pain threshold; NS = not significant; PPT = pressure pain threshold; TDT = tactile detection threshold; TPT = tactile pain threshold.

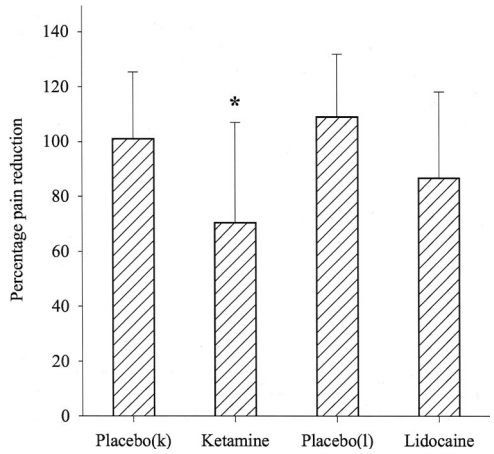

Fig. 2. Vertical bar chart showing mean pain reduction (percent) after treatment with placebo, ketamine, and lidocaine. Standard errors are given as standard deviation. Ketamine significantly reduced mean pain compared with placebo, whereas lidocaine had no effect (*$P < 0.05$, paired t test; n = 19).

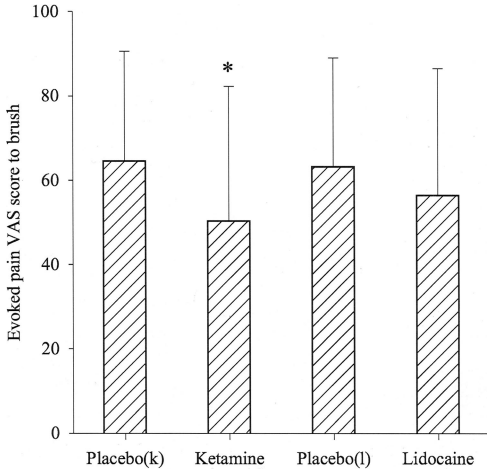

Fig. 3. Vertical bar graph showing maximum brush-evoked pain score with a foam brush. Ketamine significantly reduced pain score compared with placebo (*P < 0.05, paired t test; n = 19; error bars = standard deviation).

by repetitive pinprick stimuli at 2.0 Hz was significantly reduced by ketamine (60 ± 31) compared with saline (76 ± 22; $P < 0.001$, paired t test; n = 17). Lidocaine infusion also reduced maximum evoked pain score (66 ± 28) produced by repetitive pinprick stimuli compared with saline (75 ± 20; $P = 0.03$, paired t test; n = 17; see fig. 4).

Spontaneous Pain and Brush- and Pinprick-evoked Pain Related to Treatment

There was no correlation between mean spontaneous pain relief (1 – (mean pain 0–40 min/baseline pain)) obtained with one treatment *versus* that obtained with the other (lidocaine and ketamine; $P = 0.09$, r = 0.37, linear regression analysis; fig. 5A). In addition, no correlation was found between brush-evoked pain relief ($P = 0.78$, r = 0.07, linear regression analysis) or repetitive pinprick-evoked pain relief ($P = 0.14$, r = 0.37, linear regression analysis) related to treatment with lidocaine and ketamine (fig. 5, B and C).

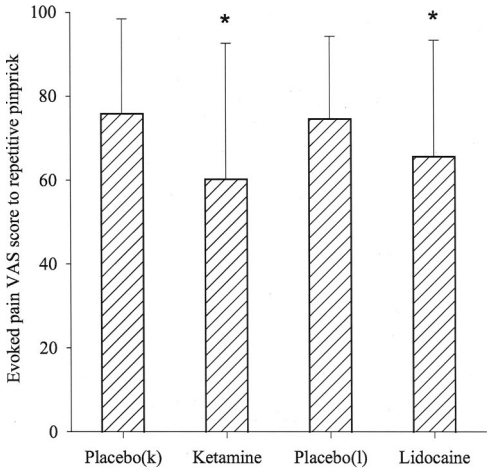

Fig. 4. Vertical bar graph showing maximum evoked pain score by repetitive pinprick stimuli at 2.0 Hz. Both ketamine and lidocaine significantly reduced evoked pain score compared with placebo (*P < 0.05, paired t test; n = 17; error bars = standard deviation).

Cold Allodynia

Seven of 19 patients (37%) experienced pain evoked by acetone drop indicating cold allodynia at the screening session. Neither ketamine nor lidocaine attenuated cold allodynia during or after the infusion has stopped.

Reaction Time

Reaction time during and at the end of infusion was measured to exclude a sedative effect of lidocaine and ketamine as an explanation of our results. Reaction time was measured in 18 patients in the lidocaine group, ketamine group, and placebo-ketamine group and in 19 patients in the placebo-lidocaine group. Reaction time measured 15 min after onset of infusion and at the end of infusion did not change (paired t test; table 3).

Plasma Concentrations of Lidocaine and Ketamine

A blood sample was obtained at the end of infusion. One patient declined to have a blood test at the end of each infusion and in another patient, the blood test was abandoned because of very small veins. The mean plasma concentration of lidocaine at the end of infusion was 3.96 ± 2.42 $\mu g \cdot ml^{-1}$ (range, 1.24–9.17 $\mu g \cdot ml^{-1}$). The mean plasma concentration at the end of infusion of ketamine was 61.03 ± 37.08 $ng \cdot ml^{-1}$ (range, 15.7–177.5 $ng \cdot ml^{-1}$). We found no relationship between plasma concentration of ketamine or lidocaine and effect on spontaneous pain or evoked pain relief (table 4).

Side Effects

No serious side effects were observed. One patient (patient 6) was excluded from the study during the first treatment session because of hallucination and aggressive behavior. When the code was broken, it was revealed that he had received ketamine. Sixteen of 19 patients (84%) experienced side effects from lidocaine, compared with 2 of 19 (11%) in the placebo group. Sixteen of 19 patients (84%) experienced side effects from ketamine infusion compared with 3 of 19 patients (16%) in the placebo group. All side effects were graded as mild to moderate. Table 5 shows the side effects.

Discussion

This study of a well-defined group of patients with peripheral nerve injury associated with spontaneous and evoked mechanical pain showed that both the NMDA-receptor antagonist ketamine and the sodium channel blocker lidocaine modulated not only spontaneous pain[25] but also evoked pain when administered acute

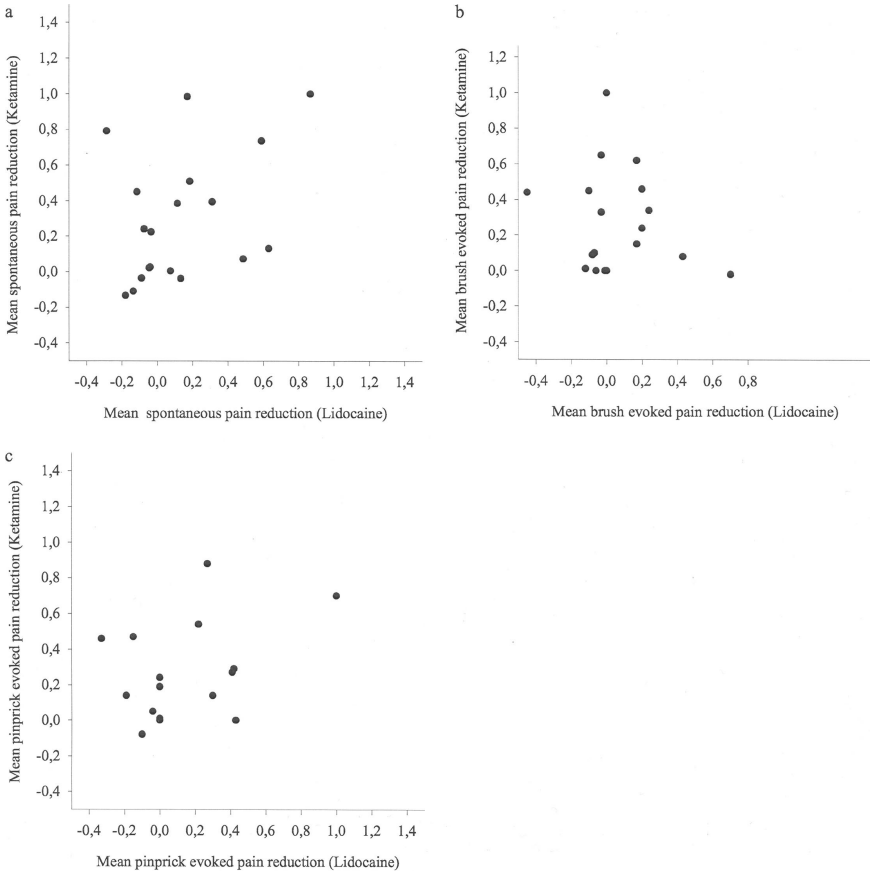

Fig. 5. (*A*) Regression plot of mean spontaneous pain reduction after ketamine and lidocaine treatment. There was no correlation between the two parameters (r = 0.40, *P* = 0.09; n = 19). (*B*) Regression plot of mean pain reduction to brush stimuli after ketamine and lidocaine treatment. There was no correlation between the two parameters (r = 0.78, *P* = 0.07; n = 19). (*C*) Regression plot of mean pain reduction to repetitive pinprick stimuli at 2.0 Hz after ketamine and lidocaine treatment. There was no correlation between the two parameters (r = 0.37, *P* = 0.14; n = 17).

and systemically. The fact that both ketamine and lidocaine had an effect indicates that both sodium channels and NMDA receptor-linked systems can be involved in pain-generating mechanisms in patients with peripheral nerve injury pain. The differential effect of ketamine and lidocaine on both spontaneous and evoked pain in a given patient suggests that the underlying pain mechanisms are pharmacologically separable and that similar symptoms may have different mechanisms and can not be used for a mechanism-based treatment based on sensory symptoms. However, our results support a mechanism-based diagnosis based on drug effect and also point to the possibility of using specific drugs as a diagnostic test to guide therapy. The present findings are in accordance with previous observations in capsaicin-induced secondary hyperalgesia demonstrating the ability of ketamine to reduce areas of pinprick- and brush-evoked hyperalgesia, whereas only the area of pinprick hyperalgesia was reduced by systemic lidocaine.[16]

Methodological Issues

The doses of ketamine and lidocaine used are rather high, raising the question of whether the observed effects of these drugs are nonspecific. We consider this possibility to be unlikely. The doses used in the present study are similar to doses used by others. We measured both side effects and reaction time. The side effects from ketamine and lidocaine used were similar, and there was no difference of reaction time in any treatment session, suggesting that the adverse effects do not affect study outcome. The plasma concentration of ketamine was much below the plasma concentration that previously was shown to be associated with hallucinations, sedations, and light-headedness.[28] A nonspecific action can not be excluded, but the fact that the pharmacology of brush-evoked and pinprick-evoked hyperalgesia can be distinguished argues against a nonspecific action.

The existing drug treatments for neuropathic pain that these patients had before and during the trial may affect

Table 3. Reaction Time Measured 15 Minutes after Infusion Started and at the End of Infusion

	Lidocaine	Placebo	*P* Value	Ketamine	Placebo	*P* Value
15 min	259 ± 36 ms	250 ± 38 ms	NS	278 ± 66 ms	246 ± 30 ms	NS
31 min	266 ± 64 ms	239 ± 26 ms	NS	253 ± 63 ms	240 ± 27 ms	NS

NS = not significant.

Table 4. Relationship between Treatment Plasma Concentrations and Spontaneous Pain and Evoked Pain Relief

	Lidocaine			Ketamine		
	Spontaneous Pain	Brush-evoked Pain	Pinprick-evoked Pain	Spontaneous Pain	Brush-evoked Pain	Pinprick-evoked Pain
r	0.23	0.25	0.24	0.20	0.16	0.01
P Value	0.37	0.32	0.31	0.45	0.52	0.96

outcome and may confound results. The existing drug treatment was unchanged for 1 week before inclusion and during the entire study period. Only 3 of 20 patients received drugs with sodium channel properties. If the given oral drug treatments had an influence on results of the intravenous treatments, they would tend to underestimate the significant findings obtained. In the present study, one of the patients who received drugs with sodium channel properties was a responder to lidocaine treatment, whereas two were responders to ketamine. Taken together, it is unlikely that the given oral treatments influenced the results obtained.

Ketamine Effect on Spontaneous and Evoked Pain

Ketamine is assumed to produce its effect by blocking NMDA-receptor ion channels in a noncompetitive fashion. Previous studies have shown that ketamine at doses similar to the ones used in the present study can antagonize evoked pain produced either by brush or repetitive pinprick stimuli in experimental skin sensitization produced by burn injury,[17,29] by capsaicin,[16,30] and in patients with different types of nerve injury pain.[20,22] In the present study, the effect of ketamine reduced both spontaneous and evoked pain to brush and pinprick at a mean plasma concentration of 61 ng·ml^{-1}. Others have shown a reduction in stroking pain score in a dose-dependent manner with the use of ketamine in neuropathic pain patients at plasma concentrations levels similar to those in the present study,[31] and in human experimental capsaicin induced hyperalgesia, ketamine at doses between 50 and 150 ng·ml^{-1} reduced mechanical hyperalgesia.[28] Both spontaneous and evoked pain may depend on peripheral and central mechanisms,[32–38] and because NMDA receptor sites have been demonstrated peripherally and centrally, we can not determine where the drugs exerted their effects. Consistent evidence exists to indicate that ketamine antagonizes experimental hyperalgesia in both animals and humans by exerting its effect centrally. However, it is more unclear if ketamine also has a peripheral action. Warncke *et al.* [39] demonstrated an effect of peripheral administered ketamine on burn-injured secondary hyperalgesia, whereas we have been unable to see an effect of peripheral ketamine on evoked pain produced by intradermal capsaicin.[40]

Table 5. Number of Patients Who Experienced Side Effects from Each Treatment

Side Effect	Lidocaine	Placebo (Lidocaine)	Ketamine	Placebo (Ketamine)
Tiredness	7		5	1
Nausea	4		1	1
Feeling drunk	3		2	
Paresthesia	3		4	1
Blurred vision	3		2	
Dizziness	2		4	1
Changed taste	3		2	
Dysarthria	3		1	
Headache	2	1		1
Dry mouth	2	1	3	
Fear		1		1
Euphoria			1	
Tinnitus			1	

Lidocaine Effect on Spontaneous and Evoked Pain

Lidocaine is an unspecific sodium channel blocker acting both peripherally and centrally.[41–43] At doses similar to the one used here, the sodium channel blocker has shown efficacy in experimental models of nerve injury pain in rats and in humans.[13,14,16,44,45] Consistent with the present study, lidocaine also has been able to antagonize pain produced by nerve injuries such as in amputation and postherpetic neuralgia.[23,26,46] In the present study, lidocaine had an effect only on pinprick-evoked pain, but failed to reduce spontaneous pain. This finding is in contrast to other studies. One possible explanation is that the evoked pain elicited 20 min after onset of infusion produced aftersensations[47] that could obscure a potential effect and precluded us from seeing it. This notion is supported by the relatively small pain-relieving effect observed with ketamine and, in fact, the increase of spontaneous pain produced by saline in both experiments. As for ketamine, we are not able to distinguish a peripheral action from a central action. We attempted to separate patients into two groups depending on whether they were sensitized peripherally. We used a principle previously used by others[6,48] in which peripheral sensitization was defined as a reduced detection threshold on the affected painful side *versus* the nonaffected side. We failed to see any difference in responder rate between the two groups, indicating that lidocaine was equally effective in patients with and without peripheral sensitization. These findings suggest that lidocaine may have exerted its effects peripherally or centrally. Based on the relatively small effect observed with lidocaine in the present study, we can not exclude that the dose used was too small to produce an effect.

However, based on plasma levels of lidocaine, we consider this possibility less likely because the concentration was at a level where effects have been observed in another trial.[23]

Sodium Channels and NMDA Mechanisms in Nerve Injury

In the present study, we compared in individual patients the action of lidocaine and ketamine. The fact that there was no correlation between pain relief obtained with the sodium channel blocker and the NMDA receptor antagonist in individual patients suggests that the pain-generating mechanisms are pharmacologically distinguishable in the individual patient. This is similar to findings observed in postherpetic neuralgia patients, where the effect of one analgesic (opioids) could not be separated from the effects obtained with other analgesics (tricyclic antidepressants) in individual patients.[27]

In a recently published study, it was suggested that symptoms at least in part can predict the outcome of a specific treatment.[26] In nerve injury pain, including postherpetic neuralgia with associated mechanical allodynia, a pain-relieving effect of systemic lidocaine was found, suggesting that mechanical allodynia may be predictive for a positive outcome with a sodium channel blocker.[26] We failed to see such an effect. The reason for this difference is not clear. One possibility is that the patients were different in terms of underlying mechanisms. In the present study, patients experienced pain and sensory disturbances after a peripheral nerve injury caused by either a trauma or surgery. Despite differences in underlying mechanisms at the axon level, we believe that the present series of patients represent a clinically homogeneous group. They all had allodynia and pinprick hyperalgesia consistent with central sensitization and decreased thermal and tactile sensation, indicating peripheral nerve injury. The heterogeneity of patients often seen in controlled clinical trials may be one of the reasons for different findings to similar treatment in controlled clinical trials. Our results are in accordance with the finding that neither allodynia nor hyperalgesia could predict efficacy of oral imipramine or gabapentin.[49] Side effects were observed in both experiments. The side effects were more common to lidocaine and ketamine than saline, but the number of individuals with psychotropic side effects (tiredness, dizziness, euphoria, and drunkenness) was almost similar in those receiving ketamine and lidocaine (table 5). This notion, together with the facts that the two experiments were performed in a randomized order and that the treatment in each experiment was randomized, argues against an insufficiently blinding procedure. As pointed out by others, disturbing side effects may limit the usefulness of these agents.[25]

In conclusion, spontaneous pain was modulated in a different way by lidocaine and ketamine. The differential effect of ketamine and lidocaine on evoked pain seen in individual patients in the present study suggests that mechanical hyperalgesia is mediated by different mechanisms. Furthermore, it is not possible to predict the outcome of different treatment from quantitative sensory testing before treatment even in a homogeneous group of patients with nerve injury and mechanical hyperalgesia.

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