Chronic Phantom Limb Pain: The Effects of Calcitonin, Ketamine, and Their Combination on Pain and Sensory Thresholds

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BACKGROUND: Calcitonin was effective in a study of acute phantom limb pain, but it was not studied in the chronic phase. The overall literature on *N*-methyl-D-aspartate antagonists is equivocal. We tested the hypothesis that calcitonin, ketamine, and their combination are effective in treating chronic phantom limb pain. Our secondary aim was to improve our understanding of the mechanisms of action of the investigated drugs using quantitative sensory testing.

METHODS: Twenty patients received, in a randomized, double-blind, crossover manner, 4 IV infusions of: 200 IE calcitonin; ketamine 0.4 mg/kg (only 10 patients); 200 IE of calcitonin combined with ketamine 0.4 mg/kg; placebo, 0.9% saline. Intensity of phantom pain (visual analog scale) was recorded before, during, at the end, and the 48 h after each infusion. Pain thresholds after electrical, thermal, and pressure stimulation were recorded before and during each infusion.

RESULTS: Ketamine, but not calcitonin, reduced phantom limb pain. The combination was not superior to ketamine alone. There was no difference in basal pain thresholds between the amputated and contralateral side except for pressure pain. Pain thresholds were unaffected by calcitonin. The analgesic effect of the combination of calcitonin and ketamine was associated with a significant increase in electrical thresholds, but with no change in pressure and heat thresholds.

CONCLUSIONS: Our results question the usefulness of calcitonin in chronic phantom limb pain and stress the potential interest of *N*-methyl-D-aspartate antagonists. Sensory assessments indicated that peripheral mechanisms are unlikely important determinants of phantom limb pain. Ketamine, but not calcitonin, affects central sensitization processes that are probably involved in the pathophysiology of phantom limb pain.

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Phantom limb pain is not a rare consequence of amputation; its estimated prevalence among amputees ranges from 30% to 81%.[1] In a study on upper phantom limb pain, the prevalence was 51%, with 64% of patients reporting moderate to very strong suffering.[2]

Although there is a positive correlation between intensity of preamputation pain and incidence of phantom limb pain 3 mo after amputation,[3] perioperative epidural analgesia did not prevent the development of phantom limb pain in a randomized, controlled trial.[4] The perioperative infusion of the *N*-methyl-D-aspartate (NMDA) antagonist, ketamine, did not affect acute postoperative pain or the incidence of phantom limb pain at 6 mo.[5] There is no scientifically validated prevention modality for phantom limb pain.

Few randomized, controlled trials on the treatment of phantom limb pain have been published. The anticonvulsant, gabapentin, was superior to placebo in a 6-wk crossover study.[6] In a recently published study, the authors found no benefit of gabapentin compared with placebo given on the first postoperative day after amputation and continued for 30 days.[7] IV morphine, but not lidocaine, decreased phantom limb pain in a crossover, placebo-controlled trial.[8] Oral morphine was also effective, with pain reduction correlating with a decrease in cortical reorganization.[9]

In a crossover study on patients who developed phantom limb pain within 7 days of amputation, calcitonin was superior to placebo for reducing phantom limb pain.[10] The literature on NMDA antagonists is equivocal. Ketamine, compared with placebo, provided better relief of phantom limb pain.[11] Dextromethorphan was effective in a study on pain in eight cancer amputees.[12] However, memantine was not

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superior to placebo in patients with phantom limb pain in three investigations.[13–15]

In the present study, conducted on patients with chronic phantom limb pain, we tested the following main hypotheses: (1) calcitonin provides better pain relief than placebo; (2) ketamine provides better pain relief than placebo; (3) the combination of calcitonin and ketamine provides better pain relief than either drug alone. A secondary aim of the study was to improve our understanding of the mechanisms of action of the investigated drugs on phantom limb pain using a multimodal sensory test procedure.

METHODS

Target Population

The study was approved by the ethics committee of the University of Bern. All subjects provided written informed consent.

Patients with phantom limb pain at either the upper or lower extremity due to either surgical or traumatic amputation were recruited. Phantom limb pain was defined as pain perceived at parts of an extremity that were no longer present. The subjects were recruited from patients referred to the Division of Pain Therapy of the Department of Anesthesiology of the University Hospital of Bern (n = 4) and by advertisements in local newspapers (n = 16).

Inclusion was made by phone call performed by a study physician. The mean pain intensity for 48 h preceding the phone call had to be at least 3.0 on the 11-point numerical rating scale 0–10, where 0 indicates no pain and 10 corresponds to the worst pain imaginable; the pain had to have been present for at least 6 mo.

Exclusion criteria were episodic pain with pain-free intervals of more than 4 h, stump pain without phantom limb pain, phantom sensations without phantom limb pain, age <18 yr or older than 85 yr, and any contraindication to calcitonin or ketamine.

Medications

Originally, we intended to test calcitonin, the combination calcitonin–ketamine, and placebo. After analyzing 10 patients, a preliminary data analysis was performed by a physician not involved in the testing. No effect of calcitonin was found, whereas the combination was superior to placebo. To investigate whether the effect of the combination was the result of combining the two drugs or rather could be attributed to ketamine alone, we introduced a fourth session with ketamine alone after receiving approval by the ethics committee. Thus, only the last 10 patients received ketamine alone.

Each patient received in different sessions an IV infusion of: (1) 200 IE of calcitonin (Miacalcic®, Novartis Pharma, Bern, Switzerland); (2) racemic ketamine 0.4 mg/kg (Ketalar®, Pfizer, Zürich, Switzerland) (only 10 of 20 patients); (3) 200 IE of calcitonin combined with ketamine 0.4 mg/kg; (4) 0.9% saline. Each medication was diluted with 0.9% saline to a total volume of 20 mL, and infused over 1 h with a constant rate of administration using an infusion pump. The minimum time between two consecutive infusions was 48 h. In the combination session, each solution was infused with a separate syringe and pump. For the other three sessions, a 0.9% saline infusion was added to the study medication, so that at each session two blinded infusions were administered concomitantly.

During infusion, we recorded a sedation score from 0 to 4, where 0 = no impairment; 1 = patient feels tired, eyes are open; 2 = patient with eyes closed, eye opening if called by name; 3 = patient sleeps, eye opening only after painful stimulus; 4 = no eye opening during painful stimulation every 5 min. If the sedation score reached 3 or 4, we stopped both infusions until recovery to a score of 2 or less was achieved and started the infusions again with 50% of the previous flow rate. At the same time points, patients were asked whether they suffered from nausea, dizziness, or felt other side effects.

The order of administration of the four study medications was determined by randomization, which was performed by drawing lots by a person not otherwise involved in the study. This person prepared the solutions and stored them in a refrigerator immediately before the start of the examinations. The medication was administered in a double-blind manner, i.e., neither the investigator performing the experiment nor the patients were aware of the solutions infused. One caution remains, in some cases drug-related side effects occurred (see Results), which rendered blinding of the physician performing the tests and the patient questionable.

During the infusion, noninvasive arterial blood pressure (measured every 5 min), electrocardiogram, and oxygen saturation using pulse oximetry were monitored continuously.

Main Outcome: Pain intensity

At the beginning of the first session, patients were asked to quantify the intensity of their pain at rest on a 10-cm visual analog scale (VAS), where 0 indicates no pain and 10 corresponds to the worst pain imaginable. If they suffered repetitive spontaneous pain attacks, the number of attacks a day and the pain intensity of these short attacks were quantified. We recorded the following values: $VAS_{max\ before}$ (maximal pain experienced during the 48 h preceding the first session) and $VAS_{mean\ before}$ (mean pain intensity experienced during the 48 h preceding the first session). During the experiment, the VAS values were recorded at the following time points: VAS_{before} (pain at the start of the infusion); VAS_{during} (pain 30 min after start of the infusion); VAS_{after} (pain at the end of the infusion, i.e., 60 min after start of the infusion). At the end of each session, the subjects received a pain diary

and were asked to note in it the pain intensity every 4 h during the time between two sessions. For the following sessions, $VAS_{mean\ before}$ was calculated and $VAS_{max\ before}$ was taken from the values noted in the pain diary. Similarly, the mean pain intensity during the 48 h after the experimental session ($VAS_{mean\ after}$) and the maximal pain experienced during the 48 h after each session ($VAS_{max\ after}$) were recorded.

A response to therapy was defined as a reduction of at least 50% in pain intensity after the end of the infusion (VAS_{after}) compared with pain intensity preceding the infusion (VAS_{before}).

Secondary Outcomes: Sensory Assessments

General Procedure

All measurements were usually performed in the anterior aspect of the stump, in a skin area where no hyposensitivity was present. Measurements at the contralateral extremity were performed in the same plane (anterior aspect of the extremity), with the same deviation from the midline of the extremity and as much distal as the corresponding stump skin area. The test locations were marked on the skin with an indelible pencil to recognize them during the session and to perform required repeated measurements at the same spot. Before each infusion, all of the tests were performed on the subjects for training purposes. When the subjects were familiar with the procedures, the experiment was started. All tests were performed at each session before the start and during the infusion (beginning 30 min after the start of the infusion). The duration of testing was 25–30 min. For each of the test modalities described below, three determinations were made and the average of these three measurements was used for data analysis.

Electrical Stimulation

Electrical stimulation was performed through bipolar surface Ag/AgCl-electrodes (cutaneous electrical stimulation) filled with electrode gel (interelectrode distance approximately 2 cm) or IM needle electrodes (IM stimulation) placed as described in the section "General Procedure." The cutaneous electrodes were left in place, and the needle electrodes were fixed by tape and also left in place during the whole session.

A 25 ms, train-of-five, 1 ms, square-wave impulse (perceived as a single stimulus) was delivered by a computer-controlled constant current stimulator (University of Aalborg, Denmark). Repeated stimuli of constant intensity may evoke an increase in the intensity of perception, so that the latter stimuli are perceived as painful.[16] This phenomenon, called "temporal summation," reflects neuronal facilitation processes in the central nervous system.[16,17] The temporal summation model, therefore, provides information on the central integrative mechanisms of sensory processing. To elicit temporal summation, the above-described stimulus was repeated five times with a frequency of 2 Hz, at constant intensity.[16] The current intensity of the five constant stimuli was increased from 0.5 mA in steps of 0.05–0.25 mA, until the subjects felt pain during the five electrical bursts (pain threshold) and until the patient reported a further increase as not tolerable (pain tolerance).

Heat Stimulation

The computer-driven Thermotest (Somedic AB, Stockholm, Sweden) was used. A thermode with a surface of 25 × 16 mm was applied to the skin. The temperature of the thermode was continuously increased from 30°C to a maximum of 52°C at a rate of 2.0°C/s. The subject was asked to press a button when the stimulus perception turned to a painful sensation (heat pain detection threshold). The procedure was then repeated and the patient was asked to press the button when she or he perceived that the pain had reached an intolerable level (heat pain tolerance threshold). At those points, the temperature was recorded by the software and the thermode cooled to 30°C. The thermode also cooled to 30°C even if the threshold was not reached at 52°C. In this case, 52°C was considered as threshold.

Pressure Stimulation

Pain detection and tolerance thresholds were measured with an electronic pressure algometer (Somedic AB). The probe had a surface area of 64 mm^2. The pressure was increased from 0 at a rate of 30 kPa/s to a maximum pressure of 1500 kPa. Pain detection threshold was defined as the point at which the pressure sensation turned to pain. Pain tolerance threshold was defined as the point at which the subject felt the pain was intolerable. The subjects were instructed to press a button when these points were reached. The algometer displayed the pressure intensity at which the button was pressed. If the subjects did not press the button at a pressure of 1500 kPa, this value was considered as threshold.

Statistical Analysis

Data were presented as median and (range) if not otherwise stated. SigmaStat for Windows version 3.01 software (Systat Software, Inc., Point Richmond, CA) was used to perform all statistical tests.

Data pertaining to changes in pain intensity (VAS) in all 20 subjects in the three treatment sessions (placebo, calcitonin, combination of calcitonin and ketamine) were analyzed by two-way repeated measure analysis of variance (ANOVA) on ranks with time and treatment as the two factors of repetition. Changes of VAS after all four treatment sessions (placebo, calcitonin, ketamine, and the combination of calcitonin–ketamine) were analyzed by one way ANOVA. It was not possible to analyze the absolute data (before–after, different treatments) by using the two-way repeated measures ANOVA because the first 10 patients did not receive ketamine treatment (see Methods, Medications) and therefore there were too many missing values to run the test.

Table 1. Demographic Data and Reasons for Amputation

Patient	Gender	Age (yr)	BMI	Duration phantom limb pain (yr)	Amputation	Reason of amputation	Mean pain	VAS mean	VAS max	Pain attacks	VAS attacks	Medication
1	M	31.7	25.8	4.1	UA	AC	3.0	1.7	4.5	1–2/wk	8.0	
2	F	54.6	25.3	2.4	LL	PA	3.5	3.0	7.2	None	—	O
3	M	63.5	36.3	13.0	TH	AC	3.0	2.1	4.6	1–2/mo	8.3	NSA
4	M	66.1	19.7	11.0	UA	AC	3.0	2.0	4.1	1–2/mo	6.6	
5	M	55.5	21.3	23.0	TH	PA	5.0	5.1	8.1	None	—	
6	F	58.4	25.5	14.0	TH	P	7.5	7.5	9.2	None	—	A, O, TA
7	M	55.1	24.0	30.0	TH	AC	4.5	3.9	4.0	1/wk	8.8	NSA
8	F	72.7	25.8	3.3	LL	PA	5.0	5.2	6.0	1/wk	8.3	NSA, O, TA
9	M	66.6	32.1	11.0	LL	DM	4.0	3.5	7.1	4/d	10.0	O, TA
10	M	33.3	25.3	11.0	LL	AC	3.5	2.6	9.1	2–3/mo	9.1	C, NSA
11	M	80.9	26.4	1.7	TH	PA	3.0	2.9	5.0	None	—	O
12	M	24.6	28.7	6.3	LL	AC	3.5	3.4	5.0	None	—	
13	M	69.9	25.5	32.3	TH	AC	8.0	8.1	9.0	None	—	A, NSA, TA
14	F	61.4	24.5	10.8	TH	MT	3.5	3.4	4.0	1/d	7.0	NSA
15	F	19.3	22.1	7.2	LL	MT	7.0	6.9	9.0	14/d	7.5	NSA, TA
16	M	71.9	21.7	8.9	UA	PA	5.0	5.3	8.0	1/d	9.5	A, NSA, O
17	M	48.5	21.6	0.9	UA	AC	6.0	6.0	7.0	4/d	8.0	
18	M	33.9	29.5	20.2	TH	AC	3.5	2.9	5.0	None	—	NSA
19	M	65.0	26.4	7.3	UA	AC	5.0	4.6	5.5	None	—	O
20	M	55.3	19.2	29.8	TH	AC	7.5	6.3	9.0	None	—	
Median		57.0	25.4	10.9			4.3	3.7	6.5		8.3	

M = male; F = female; BMI = body mass index. Site of amputation: UA = upper arm; TH = thigh; LL = lower leg. Reason for amputation: AC = accident; DM = diabetes mellitus; MT = malignant tumor; PA = peripheral arterial vascular disease; P = chronic pain. Mean pain = mean pain the 48 h before inclusion on the Numerical Rating Scale. Visual Analog Scale (VAS) mean and VAS max = mean pain and maximal pain the 48 h preceding the first session. Medication: A = anticonvulsant; C = cannabis; NSA = nonsteroidal antiinflammatory drug; O = opioid; TA = tricyclic antidepressant.

Comparisons of the number of responders after the four different treatments were performed using Fisher's exact test.

Basal pain thresholds of the amputated and contralateral side were compared by Mann–Whitney Rank Sum Test. Percentage changes of pain threshold and tolerance measurements were analyzed by two way repeated measure ANOVA on ranks with side (amputated–contralateral) and treatment as two factors of repetition.

All pairwise multiple comparison procedures were performed using the Holm-Sidak method.

To calculate the sample size, we chose a difference of 2.0 in pain intensity (VAS) as the minimum desired difference among the three groups and expected a standard deviation of 2.0.[14] Setting $\alpha = 0.05$ and investigating 20 subjects, one can detect a significant difference of 2.0 with a power of $\beta = 0.8$.

RESULTS

Drop-Outs

Of the 20 patients who were enrolled in the study, one did not want to come for the last session in which he had to receive the saline infusion. He belonged to the last 10 patients, i.e., he received the ketamine-alone infusion. In two patients, it was not possible to perform the heat and electrical stimulation, respectively, in both cases during the placebo infusion, because of technical problems with the apparatus.

Descriptive Variables

Demographic data, medications, pain intensity preceding the first treatment and reasons for amputation are shown in Table 1.

No significant changes in arterial blood pressure, heart rate, and oxygen saturation during the experiments were observed. The data are not reported. No severe complication occurred.

Concerning side effects, two patients had light sedation, score 1 during placebo infusion. During calcitonin administration, facial flushing was observed in two patients, nausea without vomiting in five patients (persisting in two patients for about 24 h), light sedation (score 1) in 1 patient, and dizziness in 1 patient. During ketamine therapy, five patients had a sedation score of 2. In one case with sedation score 3, the infusions had to be stopped for 5 min because the patient fell asleep. After 5 min (recovery of consciousness), we started the infusions again with 50% of the previous flow rate. Additional minor effects with ketamine were observed in five patients as light visual hallucination, hearing impairment, and impairment of position feeling. During the combination therapy, nausea was observed in four patients (persistent for 24 h in 2 patients) and a sedation score of 1–2 in 11 patients. In one patient with sedation score 3, the infusions had to be stopped for 5 min because the patient fell asleep. After 5 min (recovery of consciousness), we started the infusions again with 50% of the previous flow rate. Dizziness occurred in nine patients. In four patients, light hallucinations, hearing impairment, and impairment of position feeling were observed. Facial flushing occurred in one patient.

The median time between two consecutive infusions was 48 h (range, 48–240 h).

Main Outcomes: Pain Intensity

The time course of VAS before, during and after the administration of the three study medications given to

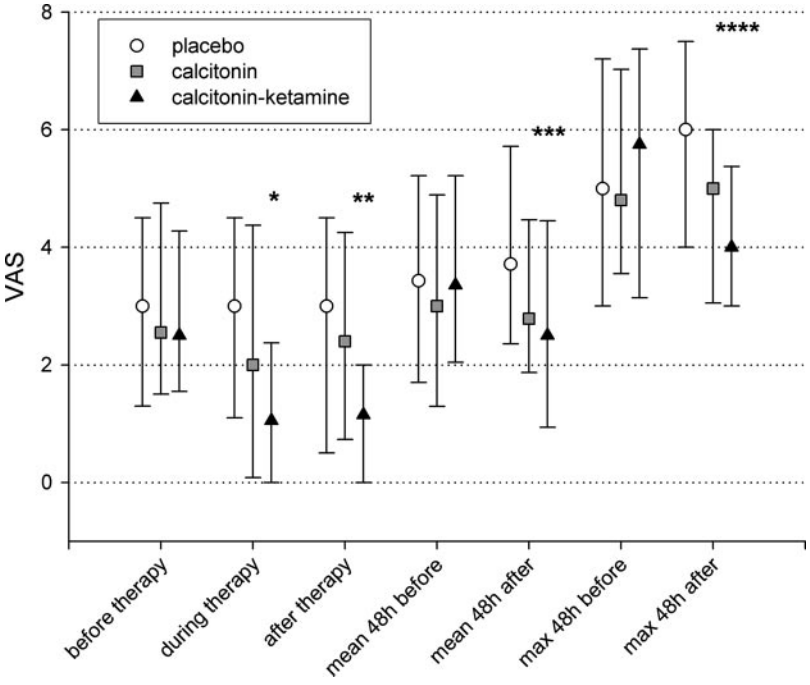

Figure 1. Time course of pain intensity Visual Analog Scale before and after the three study medications given to all 20 patients. Max 48 h before = maximal pain intensity the 48 h preceding the infusion; mean 48 h before = mean pain intensity the 48 h preceding the infusion; before therapy = pain intensity just preceding the infusion; during therapy = pain intensity after the infusion was running 30 min; after therapy = pain intensity just after the termination of the infusion; mean 48 h after and max 48 h after = mean and maximal pain intensity the 48 h after the infusion. *Combination during compared with combination before $P < 0.001$, combination during compared with placebo during $P < 0.001$ and calcitonin during $P = 0.001$. **Combination after compared with combination before $P < 0.001$, combination after compared with placebo after $P < 0.001$, combination after compared with calcitonin after $P < 0.001$. ***Combination mean after compared with combination mean before $P = 0.003$, combination mean after compared with placebo $P < 0.001$. ****Combination max after compared with combination max before $P = 0.002$ and combination max after compared with placebo $P = 0.001$.

all 20 patients are shown in Figure 1. There were no significant differences in pain intensities preceding the different treatments (VAS_{before}, $VAS_{mean\ before}$, $VAS_{max\ before}$). Only the combination reduced pain intensity significantly. During and after the infusion of the combination VAS_{during}, VAS_{after}, $VAS_{mean\ after}$, and $VAS_{max\ after}$ were significantly lower compared with the corresponding measurements VAS_{before} ($P < 0.001$), $VAS_{mean\ before}$ ($P = 0.003$) and $VAS_{max\ before}$ ($P = 0.002$). During and after the infusion of the combination, VAS_{during}, VAS_{after}, $VAS_{mean\ after}$, and $VAS_{max\ after}$ were significantly lower compared with the corresponding measurements VAS_{during} placebo ($P < 0.001$), VAS_{during} calcitonin ($P = 0.001$), VAS_{after} placebo ($P < 0.001$), VAS_{after} calcitonin ($P < 0.001$), $VAS_{mean\ after}$ placebo ($P < 0.001$), and $VAS_{max\ after}$ placebo ($P = 0.001$), respectively.

After placebo there was 1 (of 19 patients) with 50% or more reduction in pain intensity. After calcitonin administration, we had two responders (of 20), which was not significantly different from placebo. Six patients (of 10) responded to the ketamine infusion ($P = 0.003$ compared with placebo) and there were 12 (of 20) responders to the infusion of the combination, ($P < 0.001$ compared with placebo).

Because ketamine alone was administered to only 10 patients (see Methods, Medications), we present and analyzed data (see Methods, Statistics) including the infusion of ketamine separately. Figure 2 shows the percentage changes of VAS during and after all four medications. In accordance with the performed statistical analyses (see Methods, Statistics) we present the changes of VAS and not the absolute values. Calcitonin was not different from placebo, whereas

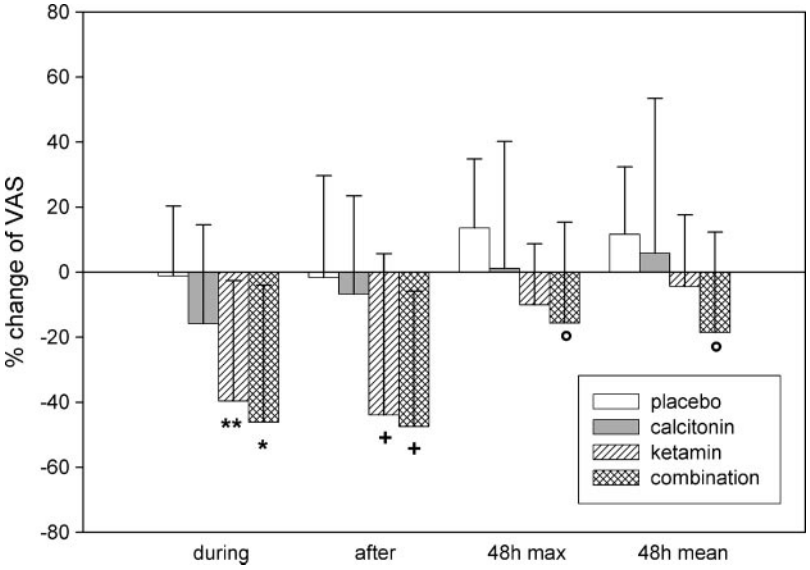

Figure 2. Percentage changes of Visual Analog Scale (VAS) during and after all four medications (ketamine only 10 patients, other medications 20 patients). During = percentage change of VAS after the infusion was running 30 min to VAS just before the infusion. After = percentage change of VAS just after termination of the infusion to VAS just before the infusion. 48 h max = percentage change of the maximal pain intensity the 48 h after the infusion to the 48 h preceding the infusion. 48 h mean = percentage change of the mean pain intensity the 48 h after the infusion to the 48 h preceding the infusion. *$P < 0.001$ to placebo and $P = 0.005$ to calcitonin. **$P = 0.004$ to placebo. +$P < 0.05$ to placebo and calcitonin. °$P < 0.05$ to placebo.

Table 2. Basal Sensory Assessments

	Cut el (mA)	Musc el (mA)	Temp (°C)	Pressure (kPa)
Thres Amp	2.1 (0.4–9.0)	1.2 (0.25–15.0)	46.3 (26.0–51.0)	256 (67–463)
Thres Cont	1.5 (0.5–5.25)	1.1 (0.25–10.25)	46.6 (35.8–51.1)	303 (165–693)*
Tol Amp	3.6 (1.0–21.0)	1.9 (0.35–31.0)	49.5 (42.6–52.0)	382 (81–1157)
Tol Cont	3.0 (0.75–12.75)	2.0 (0.35–25.25)	49.75 (40.4–52.0)	424 (240–1100)†

Experimental pain measurements. Baseline measurements on different locations. Values are presented as median (range).

Amp = amputated extremity. Cont = contralateral extremity. Tol = tolerance. Thres = threshold. Cut el = transcutaneous electrical stimulation. Musc el = intramuscular electrical stimulation. Pressure = pressure measurement. Temp = transcutaneous heat stimulation.

* Significant difference to pressure Thres Amp, $P < 0.001$.

† Significant difference to pressure Tol Amp, $P = 0.01$.

both ketamine alone and the combination of the two drugs significantly reduced VAS compared with placebo and calcitonin. No difference between ketamine alone and its combination with calcitonin was found in these 10 patients. The percentage differences of mean and maximal VAS the 48 h preceding and after the treatments respectively are also presented in Figure 2. Only the combination of calcitonin and ketamine reduced mean and maximal VAS over 48 h compared with placebo.

Secondary Outcomes: Sensory Assessments

In the basal sensory assessments,there were statistically significant differences between the amputated and the contralateral side in the threshold and tolerance measurements only for the pressure pain model. Basal sensory assessments are shown in Table 2.

Data of percentage changes during the administration of the three medications which were given to all 20 included patients were statistically analyzed and are presented in Table 3. The only statistically significant changes occurred during pressure and transcutaneous electrical pain measurements. There were significant changes in pressure thresholds ($P = 0.006$) and tolerances ($P = 0.005$) with all three study medications at the amputated compared with the contralateral side. There was a greater change in the pain threshold measured by transcutaneous electrical stimulation after the administration of the combination (calcitonin and ketamine) compared with placebo ($P = 0.007$) and calcitonin ($P = 0.012$). Similarly, there was a marked change in pain tolerance measured by transcutaneous electrical stimulation after the administration of the combination compared to placebo ($P = 0.01$).

As mentioned before (see Methods, Medications), ketamine alone was given to only 10 patients and therefore we present data including the infusion of ketamine (patients receiving all four infusions) separately. Percentage changes in sensory thresholds during administration of all four study medications are presented in Figure 3(a–d). Several values are missing. Because power is lacking, we did not further analyze these data. Thus, we did not quantify the difference between ketamine and the combination medication.

DISCUSSION

Main Outcome: Pain Intensity

We found that ketamine and the combination of calcitonin and ketamine, but not calcitonin, reduced the intensity of phantom limb pain during and after the administration of the drugs compared with placebo. The combination of calcitonin with ketamine was not superior to ketamine alone. Ketamine and the

Table 3. Percentage Changes of Experimental Pain Measurements During the Three Therapies (all 20 Patients) Compared with the Value Before Each Therapy

	Treatment	Temp delta (%)	Pressure delta (%)	Cut el delta (%)	Musc el delta (%)
Thres Amp	Placebo	0.2 (−8.3–6.4)	5.9 (−50.6–86.1)*	5.1 (−25.0–120.0)	2.4 (−66.4–123.1)
	Calcitonin	0.0 (−12.4–11.0)	16.2 (−50.3–82.1)*	0.0 (−60.0–286.4)	14.3 (−55.6–114.3)
	Calcitonin-Ketamine	0.5 (−8.4–11.8)	16.4 (−19.8–184.6)*	38.6 (−42.9–190.9)†	20.0 (−41.7–120.0)
Thres Cont	Placebo	−2.1 (−15.5–22.0)	−6.1 (−46.6–101.2)	−0.3 (−65.0–53.3)	17.7 (−30.4–171.4)
	Calcitonin	−3.4 (−12.1–7.6)	0.5 (−29.3–46.2)	10.1 (−54.4–175.0)	−6.7 (−47.1–189.5)
	Calcitonin-Ketamine	−1.6 (−8.4–13.1)	0.6 (−34.4–66.9)	19.2 (−40.0–157.1)†	13.6 (−33.3–100.0)
Tol Amp	Placebo	−0.8 (−5.7–2.7)	7.5 (−18.1–56.6)*	6.7 (−35.5–133.3)	11.7 (−62.2–151.6)
	Calcitonin	−0.7 (−4.2–3.7)	6.7 (−31.1–152.5)*	7.0 (−57.7–238.2)	4.3 (−30.0–141.4)
	Calcitonin-Ketamine	−1.0 (−4.4–5.5)	12.8 (−19.8–86.1)*	20.2 (−48.2–289.5)†	33.3 (−29.3–123.7)
Tol Cont	Placebo	−1.1 (−12.8–5.2)	0.8 (−26.3–60.0)	0.0 (−34.5–33.3)	0.0 (−41.1–150.0)
	Calcitonin	−1.9 (−7.5–2.3)	0.8 (−12.4–95.3)	10.4 (−50.5–150.0)	3.6 (−58.0–174.2)
	Calcitonin-Ketamine	−0.6 (−5.0–6.2)	4.3 (−32.8–50.2)	29.3 (−34.8–100)†	27.3 (−26.1–135.3)

Values are presented as median (range).

Amp = amputated extremity; Cont = contralateral extremity; Tol = tolerance; Thres = threshold; Cut el = transcutaneous electrical stimulation; Musc el = intramuscular electrical stimulation; Pressure = pressure measurement; Temp = transcutaneous heat stimulation.

* Significant difference in pressure pain (thresholds and tolerances) amputated to contralateral side ($P < 0.01$).

† Significant difference of transcutaneous electrical pain (thresholds and tolerances) after calcitonin–ketamine administration compared with placebo and calcitonin ($P < 0.05$).

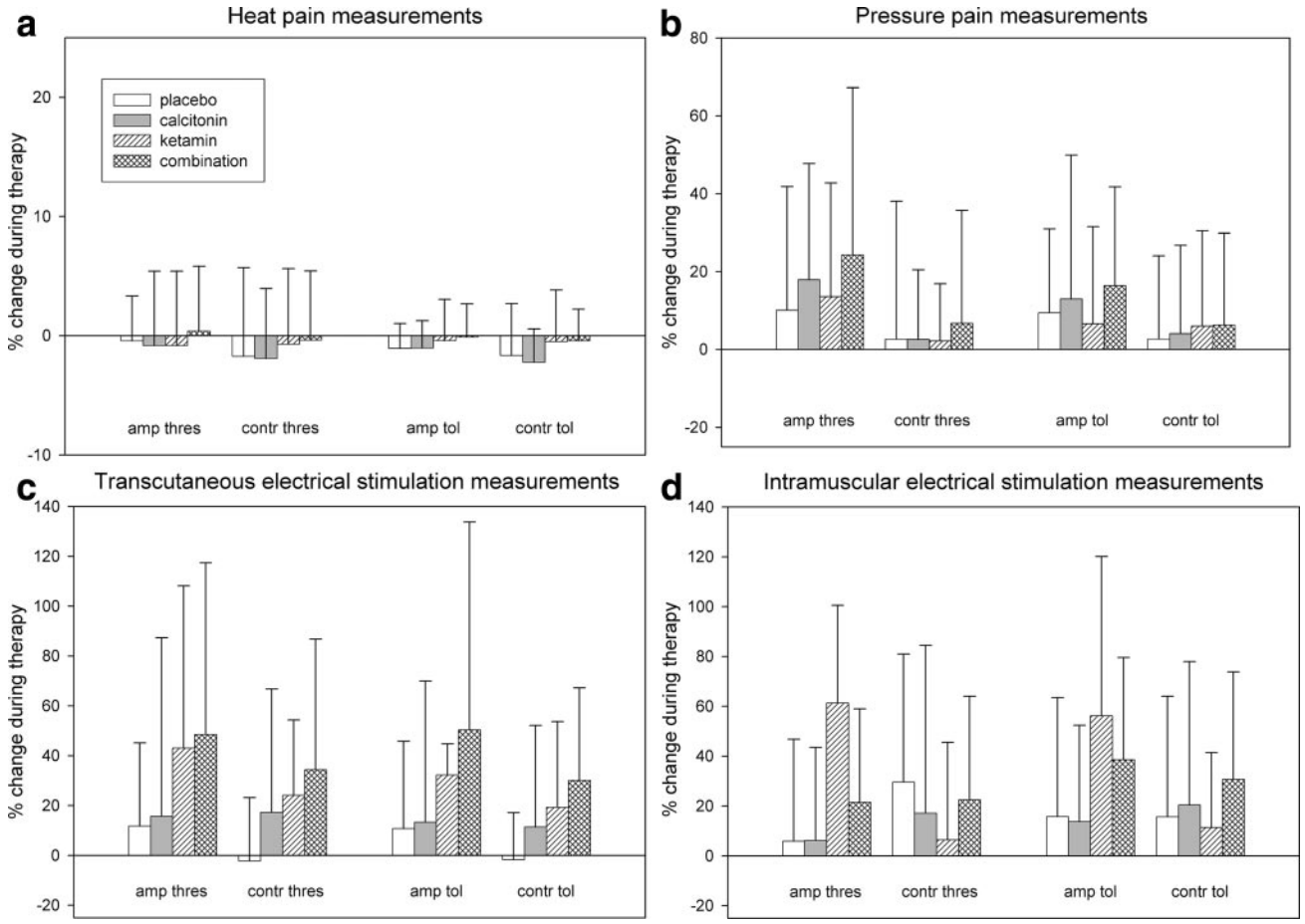

Figure 3. (a–d) Percentage changes in sensory pain thresholds and tolerances to (a) heat, (b) pressure, (c) transcutaneous electrical stimulation, (d) IM electrical stimulation during administration of all four study medications (ketamine only 10 patients, other medications 20 patients). Amp thres = percentage change of the threshold measurement at the amputated extremity during the infusion to the threshold measured before the infusion was started. Contr thres = percentage change of the threshold measurement at the contralateral extremity during the infusion to the threshold measured before the infusion was started. Amp tol = percentage change of the tolerance measurement at the amputated extremity during the infusion to the tolerance measured before the infusion was started. Contr tol = percentage change of the tolerance measurement at the contralateral extremity during the infusion to the tolerance measured before the infusion was started.

combination of calcitonin and ketamine reduced pain intensity 50% or more in 60% of patients (responders), whereas only 10% of patients were responders after calcitonin and placebo treatment. On the other hand, only the combination of the two drugs significantly reduced mean and maximal pain intensity 48 h after treatment compared with placebo. Our findings do not confirm the significant effect of calcitonin on phantom limb pain that was observed in a previous study.[10] In that study, patients with acute phantom limb pain in the early postoperative phase were treated. Conversely, our patients suffered long-term phantom limb pain (Table 1).

The development of central plasticity changes over time after amputation has not been thoroughly investigated. Moreover, the mechanisms of action of calcitonin are uncertain.[18] Therefore, it is difficult to provide compelling reasons for the differences in results between the two investigations. A possible explanation is that different mechanisms account for phantom limb pain in the acute and chronic phases, and that calcitonin may be effective only at a very early stage postamputation.

Our data seem to confirm the efficacy of ketamine in phantom limb pain.[11] Another less potent NMDA-antagonist, memantine, lacks clinical efficacy.[13–15] Because our study was initially designed to test only three study medications (see Methods, Medications) and therefore the sample size was calculated with three medications only, we cannot exclude a β error in the statistical analysis of the four treatments (including only 10 patients also receiving ketamine alone and one patient with only half of the original planned flow rate). Analyzing all patients for treatments, we found no statistical significances but a trend to a higher reduction in pain intensity caused by the combination compared to ketamine alone (Fig. 2). Therefore, we cannot conclude with certainty that the measured effect is really caused by ketamine alone. However, the lack of difference in the percentage of responders to ketamine and the combination, and the lack of effect of calcitonin, suggest that the effect of the combination

on pain intensity is only due to the action of ketamine alone. Problems with chronic use of ketamine in phantom limb pain have not been investigated. Poor oral bioavailability, concerns regarding safety and the difficult balance between clinically significant benefit and side effects may render the chronic use of ketamine problematic.[19,20] Nevertheless, because of the potential usefulness of ketamine, studies on its long-term use are desirable. Furthermore, research on the development of NMDA antagonists with a more favorable balance between analgesic and adverse effects is warranted.

A possible limitation of the study is the fact that more males than females were included and there was a very wide range of chronic pain duration (Table 1). Because of the relatively small sample size, the influence of gender and pain duration on the outcomes cannot be analyzed.

Secondary Outcomes: Sensory Assessments

Aside from pressure pain, there was no difference in any basal pain threshold between the amputated and contralateral side. This indicates that peripheral sensitization is probably not a major determinant of phantom limb pain in most patients. Central hypersensitivity to experimental pain stimuli has been repeatedly demonstrated in different chronic pain conditions.[21–24] Hypersensitivity to sensory stimulation seems to be generalized, i.e., not confined to the neuronal structures that are connected to the site of injury. For instance, hypersensitivity to stimulation of the lower limb has been repeatedly observed in patients who suffer neck pain after a whiplash injury.[21,22,25] We are not aware of studies comparing pain thresholds of patients with phantom limb pain to those of healthy controls; therefore, the contribution of central hypersensitivity to pain cannot be quantified.

Pain thresholds were unaffected by calcitonin administration, which mirrors the lack of effect of this drug on pain intensity. While the analgesic effect of ketamine was associated with a significant increase in electrical thresholds, pressure and heat stimulation remained unaffected by the drug. The effects of ketamine on different experimental pain modalities in healthy volunteers have been the focus of several investigations. Ketamine did not affect thermal pain thresholds in two different investigations,[26,27] but had an effect on heat stimulation inducing wind-up.[26] In contrast, temporal summation of painful electrical stimuli was significantly inhibited by ketamine, both after transcutaneous[28] and IM[29] stimulation. Interestingly, ketamine affected the reflex threshold to repeated, but not to single, electrical stimulation,[28] which confirms the well-known effect of this drug on central sensitization processes.[30,31] A study using oral ketamine was unable to find any effect on secondary hyperalgesia, thermal, and pressure pain thresholds.[32]

In an investigation of patients with phantom limb pain, ketamine had no effect on thermal pain thresholds, but increased pressure pain thresholds and wind-like pain evoked by repeatedly tapping the dysesthetic skin.[11] The authors concluded that stump and phantom limb pain may be generated by afferent fibers that are activated by mechanical, but not thermal, stimuli. Because we did not find changes in pressure pain thresholds, we cannot come to the same conclusion.

Taken together, our data are consistent with the lack of effect of ketamine on thermal pain thresholds in both healthy volunteers and patients with phantom limb pain. The lack of effect on pressure pain confirms the findings of an investigation of healthy volunteers,[32] but not those of a study on patients with phantom limb pain.[11] Differences in the infusion regimens and in patient characteristics may account for this discrepancy. It is possible that phantom limb pain patients are a heterogeneous population, with activation of mechanoreceptors playing a role as a primary generator of pain in some, but not all, subjects.

The effects of electrical stimulation seem more consistent, at least when temporal summation models are used. Pressure and heat stimulation primarily activate the nociceptors. Conversely, electrical stimulation activates the nerve fibers, and hence bypasses the receptors. This may minimize the confounding factor of the influence of nociceptor activation, thereby rendering the results more consistent.

In summary, the results of sensory assessment indicate that central mechanisms are more important than peripheral mechanisms as determinants of phantom limb pain. The effects of ketamine on the experimental pain modalities that we used are similar to the effects of this drug on the same stimulus modalities applied on healthy volunteers. These findings suggest that the mode of action of ketamine in patients with phantom limb pain and in normal subjects may be similar.

CONCLUSIONS

IV infusion of calcitonin is ineffective to treat chronic phantom limb pain. Ketamine seems to reduce the intensity of pain in these patients significantly. Adding calcitonin to ketamine does not confer additional benefit. Central mechanisms are more important than peripheral mechanisms as determinants of phantom limb pain. Ketamine, but not calcitonin, affects central sensitization processes that are likely involved in the pathophysiology of phantom limb pain. This study confirms the potential interest in NMDA-antagonists for the treatment of this difficult pain condition and suggests further research for the translation of this knowledge into benefits for patients.

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