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Safety-efficacy balance of S-ketamine and S-norketamine in acute and chronic pain

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Chapter 4

Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain:

A randomized, prospective, double blind,
active placebo-controlled trial

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Introduction

Fibromyalgia is characterized by chronic generalized musculoskeletal pain without a specific structural or inflammatory cause.¹ Prevalence is 2-3% with predominance for women (sex ratio 1:7).¹ There is debate whether fibromyalgia pain is neuropathic in origin. The IASP defines neuropathic pain as pain caused or initiated by a primary lesion or dysfunction in the nervous system.² Although no specific causes of fibromyalgia in the peripheral or central nervous system are apparent, fibromyalgia pain has been associated with central sensitization.^{3,4} For example, Desmeules et al. observed reduced thermal pain thresholds and a reduced spinal nociceptive flexion reflex threshold in fibromyalgia patients.³ Various mechanisms may underlie the process of central sensitization, most importantly, *N*-methyl-D-aspartate receptor (NMDAR) activation and up-regulation at spinal and supraspinal sites.⁵ A role for NMDAR activation in fibromyalgia comes from studies in which the analgesic response to a low-dose intravenous ketamine (0.1 mg/kg) test is a positive predictor for a subsequent analgesic response to oral dextromethorphan.^{6,7} Both ketamine and dextromethorphan block the NMDAR.

In the current study we investigated the effect of a short-term S-ketamine infusion on fibromyalgia pain. We assessed the effect of a 30-min infusion with a relatively high dose of S-ketamine (0.5 mg/kg, equivalent to 1.0 mg/kg racemic ketamine)⁸ on pain relief in the period following treatment. Studying the phase following treatment rather than during treatment is based on the following observations: (i) in animals, NMDAR antagonism in neuropathic pain states causes relief of spontaneous pain and allodynia outlasting the duration of *in vivo* NMDAR antagonism⁹; (ii) a short infusion with S-ketamine causes pain relief lasting for 24 h or longer in patients with Complex Regional Pain Syndrome type 1 (CRPS-1)¹⁰; (iii) treating patients with small-fiber neuropathy (due to diabetes and sarcoidosis) with a 1-h infusion with 0.5 mg/kg S-ketamine causes long-term pain relief (>> 24 h; M Niesters, unpublished observation); and (iv) a single infusion with 0.5 mg/kg ketamine produces antidepressant effect lasting one to seven days in therapy resistant major depression.¹¹ Although the latter patient population was not targeted for pain-related symptoms, we hypothesized with Zarate et al. and others that a common mechanism of action may cause both relief of the symptoms of depression and pain (i.e., blockade of the NMDAR).¹¹

We hypothesize that (i) ketamine causes greater pain relief than placebo; (ii) ketamine induces pain relief beyond the treatment period (i.e., ketamine effect is not driven by pharmacokinetics). We compared the effect of ketamine to an active placebo (the benzodiazepine midazolam) to control for occurrence of side effects during treatment allowing a proper blinding of the study.

Methods

Patients were recruited after protocol approval was obtained from the local Human Ethics Committee (Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands) and the Central Committee on Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, The Hague, The Netherlands). Informed consent was obtained according to the Declaration of Helsinki. The study was registered under number NTR1343 before recruiting at www.trialregister.nl.

Patients

Fibromyalgia patients were recruited through the outpatient clinics of the departments of Anesthesiology (pain clinic) and Rheumatology of the Leiden University Medical Center, as well as through an advertisement on the website of the Dutch Fibromyalgia Patient Association. Inclusion criteria were: fibromyalgia syndrome diagnosed according to the 1990 'American College of Rheumatology' criteria (presence of widespread pain and tenderness in at least 11 of 18 tender points on specific muscle-tendon sites)¹², age 18-75 years, spontaneous pain score of 5 or greater (based on a scale from 0 = no pain to 10 = most severe pain imaginable). Exclusion criteria were body weight > 100 kg or body mass index ≥ 35 , use of strong opioids, a score of eight or greater on the subscale of the Hospital Anxiety and Depression Scale (HADS), pregnancy or lactation, severe cardiovascular disease, psychiatric disease, allergy or co morbidities incompatible with study medication (S-ketamine, midazolam), presence of factors or other diseases that could interfere with pain scores and functionality.

Patients were allowed to continue their medication and other therapies during the 8 weeks of the study, but changes in therapy were not allowed. They were asked not to eat or drink anything at least 4 hours prior to the treatment infusion and had to refrain from grapefruit and grapefruit juice for 7 days prior to the infusion.

Study design

This study had a randomized prospective, double blind, active placebo-controlled design. Randomization into S-ketamine (Ketanest, Pfizer BV, Capelle aan de IJssel, The Netherlands) or midazolam (Synthon BV, Nijmegen, The Netherlands) treatment groups was performed after subject screening and inclusion. An independent physician performed the randomization using an electronic randomization list (downloaded from www.randomization.com). An independent physician also prepared the study medication in a blinded syringe.

The study consisted of a single treatment day at the beginning of week 1 followed by an 8-week follow-up. On the study day two intravenous catheters were placed in the hands or arms of the patient, one for drug administration and one for blood sampling. After baseline measurements, patients received an infusion (starting at $t = 0$) with either 0.5 mg/kg S-ketamine or 5 mg midazolam given over 30 minutes. This was followed by 2.5 h of measurements after which the patients were discharged. Following treatment, weekly measurements of treatment effect were obtained. At the end of the study all patients were asked which treatment they thought they had received and were next informed of their treatment. Patients given midazolam were given the possibility of receiving an open-label ketamine treatment.

Measurements on the treatment day

Spontaneous (fibromyalgia) pain

Prior to infusion on the study day, a baseline pain score was obtained using a Visual Analogue Scale (VAS). The VAS was recorded by patients on a 10-cm paper scale that ranged from 0 (no pain) to 10 (worst pain). This was recorded 3 times and averaged for further analysis. After the infusion fibromyalgia pain scores were obtained at $t = 45, 60, 75, 90, 120, 150$ and 180 minutes following the start of intravenous treatment.

Heat pain test

To compare the effect of S-ketamine on a standardized nociceptive stimulus in the study population a noxious thermal stimulus was applied with the TSA-II NeuroSensory Analyzer (Medoc Ltd., Israel). A 3 x 3 cm thermode was placed on the skin of the volar side of the forearm. The temperature was gradually increased by 0.5 °C/s, from 32 °C to a peak temperature in the range of 46 to 52 °C. Peak temperature remained for one second, after which it rapidly decreased (10 °C/s) to 32 °C. After this stimulus, a VAS score for heat pain was obtained (scale 0 to 10). Peak temperature was determined by performing a set of test experiments prior to the drug infusion. To that end, peak temperature was set at 46 °C and the VAS score was obtained. When the VAS score was < 5 a subsequent test was performed with peak temperature increased by 1 °C (max. temperature allowed = 52 °C). The temperature at which the VAS score was 5 or greater was used in the remainder of the study. The test data were discarded. Next, three baseline tests were performed and the VAS data were averaged for further analysis. Heat pain tests were performed at $t = 0$ (baseline), 45, 60, 120, and 180 min after the start of the infusion. In order to prevent adaptation or sensitization, the location of the thermode was changed after every stimulus.

Side effects

S-ketamine side effects were measured using the Bowdle questionnaire.¹³ This questionnaire consists of 13 psychotomimetic side effects that are typical for ketamine. These 13 items were scores on a numerical rating scale (NRS) ranging from 0 to 10 at $t = 0$ (baseline), 45, 60, 120 and 180 min after the start of treatment. The 13 items of the questionnaire were:

- (i) my body or body parts seemed to change their shape or position (body);
- (ii) my surroundings seemed to change in size, depth, or shape (surroundings);
- (iii) the passing of time was altered (time);
- (iv) I had feelings of unreality (reality);
- (v) it was difficult to control my thoughts (thoughts);
- (vi) the intensity of colors changed (colors);
- (vii) the intensity of sound changed (sound);
- (viii) I heard voices or sounds that were not real (voices);
- (ix) I had the idea that events, objects, or other people had particular meaning that was specific for me (meaning);
- (x) I had suspicious ideas or the belief that others were against me (suspicious);
- (xi) I felt high (high);
- (xii) I felt drowsy (drowsy);
- (xiii) I felt anxious (anxious).

Monitoring

During and following infusion the following items were monitored: heart rate, blood pressure, breathing rate and arterial hemoglobin-oxygen saturation.

Blood sampling

Venous blood samples for measurement of plasma concentrations of S-ketamine and its active metabolite S-norketamine were obtained at $t = 0$ (baseline), 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 75, 90, 120, 150 and 180 min. Plasma was separated within 15 min of blood collection and stored at -25°C until analysis. Analysis was by high performance liquid chromatography as described previously.¹⁴ The lower limit of quantitation was 10 ng/ml, the lower limit of detection 3 ng/ml for both analytes.

Measurements during follow-up

The Fibromyalgia Impact Questionnaire (FIQ)

The FIQ was chosen to measure the effect of treatment.¹⁵ This questionnaire is especially developed and validated for fibromyalgia patients and measures pain, stiffness, and activities in daily life over a period of one week. It consists of a total of 20 items that are quantified on numerical or visual analogue scales. Measurements were obtained on a weekly basis during the 8-week follow-up period (first measurement at baseline; second measurement at the end of week 1; last measurement at the end of week 8).

Data and statistical analysis

The study was powered to detect a 2-point difference in pain score during follow-up. Assuming a SD of 1.5, a power of 0.8 and α of 0.05 (two sided)¹⁶, we calculated that 10 patients per group were needed per group. To compensate for possible loss of subjects during the study we enrolled 12 subjects per group. Statistical analysis included all patients according to the intention-to-treat principle.

The demographics of the treatment groups and baseline pain scores were compared using t-tests for continuous variables and Chi-square or Fisher's exact tests for categorical data. Patients that had a pain relief of their spontaneous fibromyalgia pain of > 50% were considered responders. A linear mixed model was used to analyze pain scores (on the study day and during the 8-week follow-up), side effects (derived from the Bowdle questionnaire) and heat pain scores. Finally the VAS scores relative to baseline (Δ VAS) were compared for experimental and fibromyalgia pain at $t = 45$ and 180 min. In the analyses the time is a within-subject factor and treatment level (or pain type) is a between-subject factor. Data analysis was performed with the statistical package SPSS 16.0. P-values < 0.05 were considered significant. Data are presented as mean \pm SEM unless stated otherwise.

Results

Sixty-three patients were requested to participate in the study (Figure 1). Since 27 refused, 36 were screened of which 25 were randomized (11 did not meet the inclusion criteria). One patient refused further participation on the treatment day (prior to baseline measurements). The number of subjects treated was 24 subjects (12 in each group). The median time since diagnosis was 1.3 years (range 0.1 to 16 years), with on average 16 tender points. Patient demographics and baseline values are shown in Table 1.

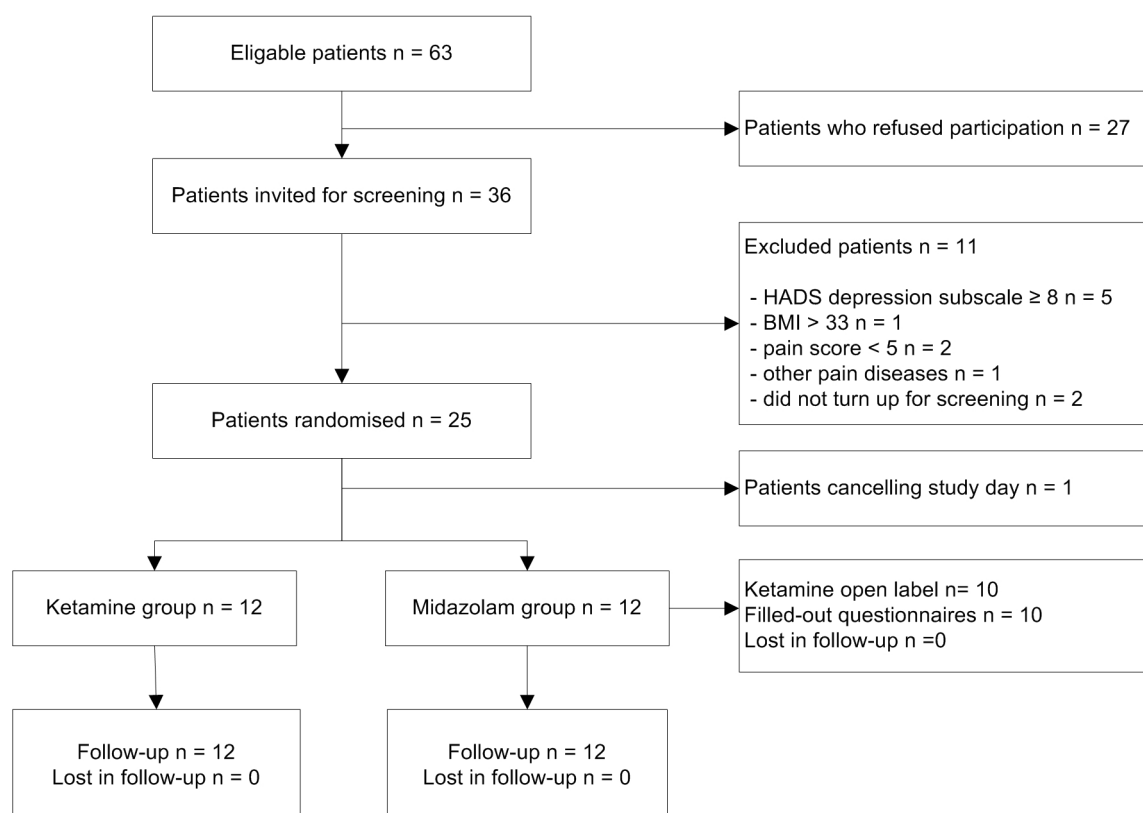


Figure 1 Study flow-chart.

Treatment effect on pain scores and side effects on the treatment day

Fibromyalgia pain

Baseline pain scores were 5.4 ± 0.6 cm in the S-ketamine group and 5.8 ± 0.4 cm in the midazolam group (ns). S-ketamine caused the reduction of fibromyalgia pain to 1.9 ± 0.8 cm ($P < 0.01$ versus baseline) at $t = 45$ and to 3.1 ± 0.8 cm at $t = 180$ min ($P < 0.01$ versus baseline) (see Figure 2). Midazolam pain scores at $t = 45$ min and $t = 180$ min were 4.4 ± 0.6 cm ($P < 0.01$) and 4.3 ± 0.7 cm ($P < 0.01$). Comparing treatments, a significant time effect was observed ($P < 0.001$) without significant treatment ($P = 0.09$) or interaction ($P = 0.10$) effects. This indicates the absence of a difference in pain relief between S-ketamine and midazolam in the treatment recovery period (i.e., $t = 45$ min to $t = 180$). In patients treated with S-ketamine VAS scores closely followed the S-ketamine plasma concentrations (Figure 2A) indicating that effect was driven by ketamine pharmacokinetics.

Table 1 Patient demographics and baseline characteristics.

	All patients	S-ketamine	Midazolam	
N women/men	23/1	11/1	12/0	ns
Age (year)	42.1 ± 11.0	39.1 ± 10.6	45.2 ± 10.9	ns
Weight (kg)	76.8 ± 13.0	79.5 ± 9.7	74.1 ± 15.6	ns
Height (cm)	170.9 ± 6.6	172.0 ± 5.6	169.8 ± 7.6	ns
Body mass index (kg/m ²)	26.2 ± 4.1	27.0 ± 4.4	25.4 ± 3.7	ns
Time since diagnosis (months) [#]	16 (1-192)	14 (1-168)	34 (1-192)	ns
Number of tender points	16.2 ± 1.9	16.7 ± 1.5	15.8 ± 2.2	ns
HADS total	9.6 ± 4.5	9.6 ± 4.1	9.6 ± 5.1	ns
HADS depression	3.5 ± 2.1	3.7 ± 2.3	3.4 ± 2.1	ns
HADS anxiety	6.0 ± 3.7	5.9 ± 3.3	6.2 ± 4.1	ns
Pain score at baseline (NRS)	7.0 ± 1.0	7.2 ± 1.2	6.8 ± 0.7	ns
Current pain medication (N)				
Paracetamol	7	3	4	ns*
NSAIDs	11	5	6	ns*
Tramadol	2	1	1	ns*
Amitriptyline	3	1	2	ns*
Duloxetine	1	1	0	ns*
Pregabalin	2	1	1	ns*

Data presented as mean ± SD.

[#] median (range); * Fisher exact test.

N = number

The number of responders did differ significantly between treatments from t = 45 to t = 60 min (Figure 3). At t = 45 min 8 patients receiving S-ketamine and 3 patients receiving midazolam had a pain reduction > 50%. Considering only the responders, S-ketamine caused pain reduction from 5.3 ± 0.8 (baseline) to 0.6 ± 0.2 cm (t = 45 min); midazolam caused pain reduction from 5.2 ± 1.9 to 1.8 ± 1.0 cm. In the S-ketamine group the number of responders declined. At t = 180 min the number of responders was 6 in the S-ketamine group (with pain score 0.8 ± 0.3 cm) versus 3 in the midazolam group (2.0 ± 0.3 cm).

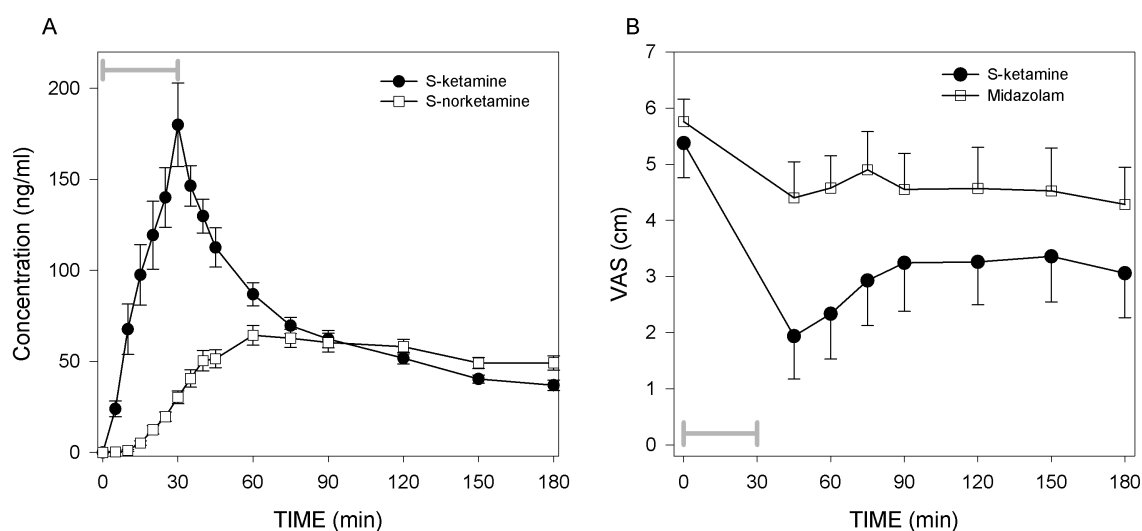


Figure 2 **A** Mean plasma concentrations of S-ketamine and S-norketamine in patients that received a 30-min S-ketamine infusion (grey bar). **B** Effect of a 30-min treatment with S-ketamine (0.5 mg/kg, closed circles, $n = 12$) and midazolam (5 mg, open squares, $n = 12$) on pain scores in fibromyalgia patients. No significant differences in pain relief between the two treatment was observed during the treatment recovery phase ($t = 45$ to $t = 180$ min). The grey bar indicates the treatment period. Data are mean \pm SEM.

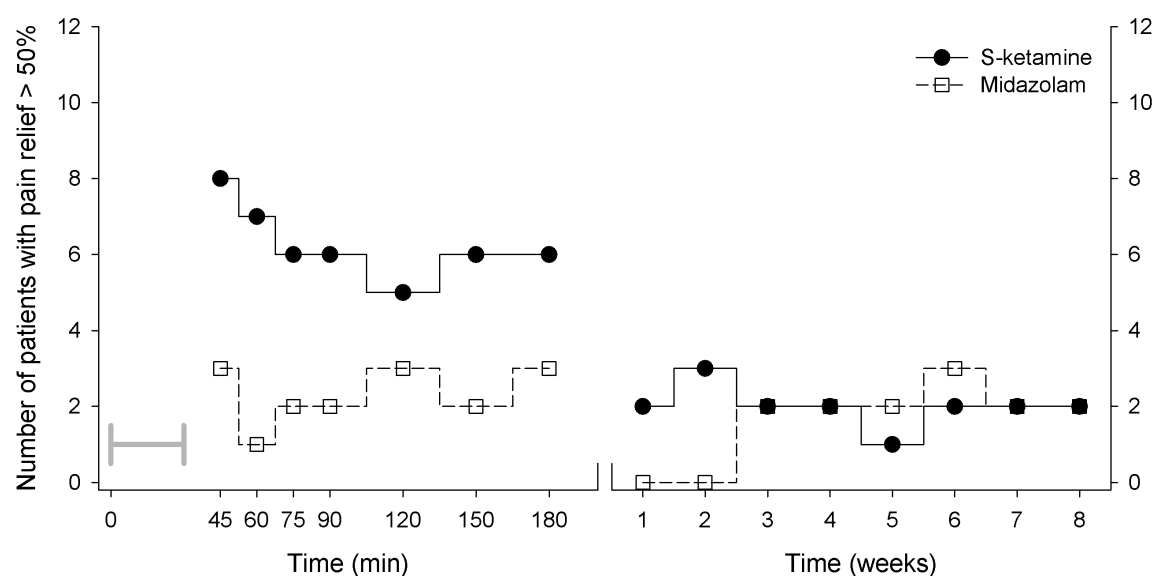


Figure 3 Number of fibromyalgia patients with pain relief > 50%. **Left** graph: data derived from the assessment of spontaneous fibromyalgia pain following treatment ($t = 45$ to 180 min following the 30-min treatment period). **Right** graph: data derived from the weekly Fibromyalgia Impact Questionnaire, which assess the mean pain score over the previous week. A difference in number of patients that had a pain score > 50% was significant at time $t = 45$ and $t = 60$ min only. The grey bar indicates the treatment period.

Experimental heat pain

Baseline heat pain intensity scores were 6.5 ± 0.3 cm and 5.4 ± 0.4 cm in the S-ketamine and midazolam groups, respectively ($P = 0.046$). Taken the difference in baseline values between groups, the treatment effects are presented relative to baseline (Figure 4). S-ketamine reduced the heat pain intensity score by 2.0 ± 0.9 cm at $t = 45$ min ($P < 0.01$ versus baseline) and 0.2 ± 0.7 cm at $t = 180$ min (ns). Midazolam effect at $t = 45$ and 180 min was -0.9 ± 0.7 cm ($P < 0.05$) and $+0.5 \pm 0.6$ cm (ns). Comparing treatments, there was a significant main effect of time ($P < 0.01$; pain intensity was significantly different at $t = 45$ min relative to baseline ($P = 0.01$) but not at $t = 180$ min). Group and interaction effects were not significant. These data indicate no difference in effect between the two treatments on experimental heat pain in the 2.5 h period following treatment.

For both treatments, no differences in Δ VAS values were observed for experimental pain versus fibromyalgia pain at $t = 45$ and 180 min (S-ketamine: main effect $P = 0.08$; midazolam: main effect $P = 0.09$).

Side effects

Pre-treatment side effects as derived from the Bowdle questionnaire were not different between treatment groups. Following infusion a significant treatment effect was observed for 5/13 items of the questionnaire: surroundings, time, reality, thoughts and high, with a significant difference between treatments at $t = 45$ min ($P < 0.05$). The highest score was for reality: 6.5 ± 1.0 (S-ketamine versus midazolam = 1.1 ± 0.7) at $t = 45$ min. The other items were not different between groups. The effect of treatment on the items high and drowsy are shown in Figure 5; high but not drowsy differed between treatments. The total Bowdle scale showed no treatment effect ($P = 0.08$) but a significant time ($P < 0.01$) and time*treatment effect ($P < 0.01$) was observed.

Vital signs

No differences in baseline values were observed between treatment groups. Baseline heart rate was 70 ± 2 per min, respiratory rate 16 ± 0.3 per min, oxygen saturation $99 \pm 0.3\%$, and mean arterial pressure 87 ± 3 mmHg. All values remained well within clinically acceptable ranges throughout the infusion and 150-min recovery period. Heart rate and blood pressure increased by about 20% during S-ketamine infusion while respiratory rate showed a 10% decrease. No changes were seen during midazolam infusion. Oxygen saturation remained $> 98\%$ during S-ketamine and midazolam infusions.

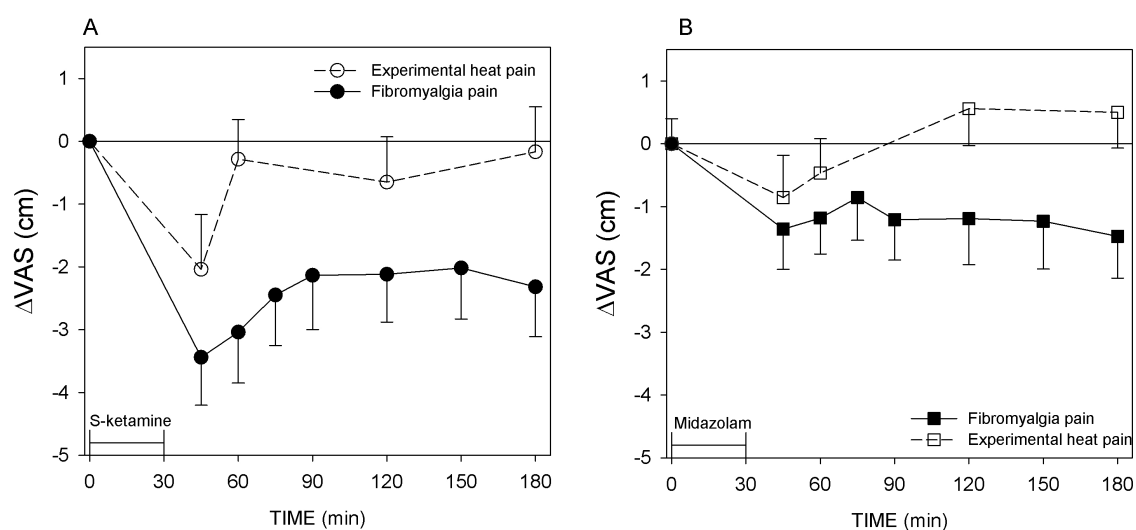


Figure 4 Effect of S-ketamine and midazolam treatment on experimental heat pain intensity scores. **A** Scores following S-ketamine treatment. **B** Scores following midazolam treatment. No differences between treatments on experimental pain scores were observed. For comparison, the effect of treatment of the fibromyalgia pain scores are included. The grey bar indicates the treatment period. Data are mean \pm SEM.

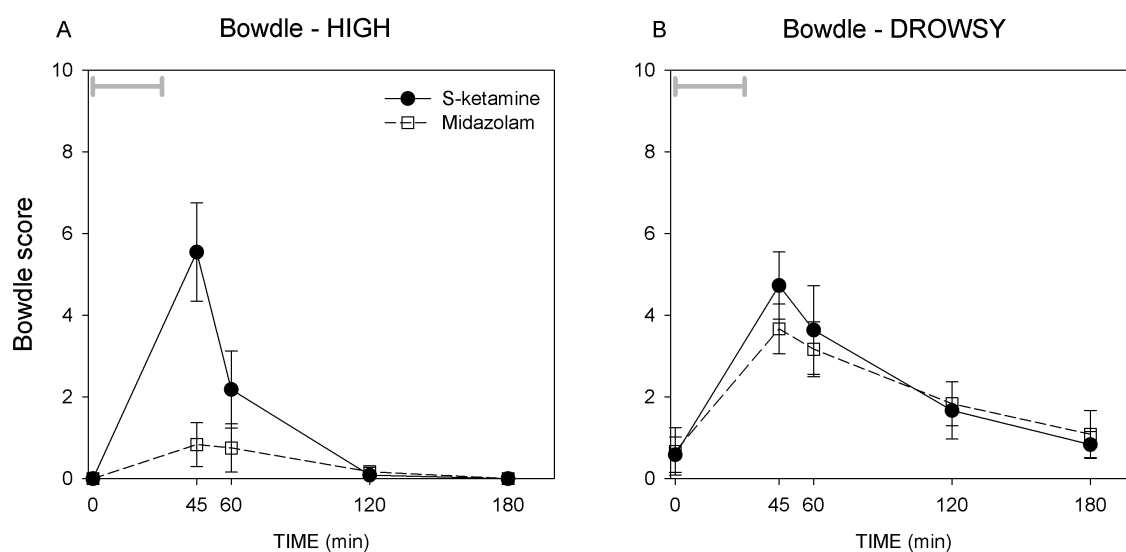


Figure 5 Effect of treatment on the Bowdle **A** high and **B** drowsy scores. A significant treatment effect was observed for high at $t = 45$ min. The grey bar indicates the treatment period. Data are mean \pm SEM.

Effect of treatment on the Fibromyalgia Impact Questionnaire in weeks 1 to 8

Baseline FIQ scores were similar between treatments: 52 ± 4 and 50 ± 3 in S-ketamine and midazolam groups, respectively. No time ($P = 0.07$), group ($P = 0.98$) or interaction ($P = 0.80$) effects were observed in weeks 1 to 8 following treatment (Figure 6). Similarly, baseline pain scores (derived from the questionnaire) were not different between S-ketamine (6.7 ± 0.6) and midazolam

(7.6 ± 0.3) treatments. The FIQ pain scores were higher than the baseline fibromyalgia pain assessment on the treatment day (instantaneous sample). The FIQ pain score is the mean pain score over the past week and these results indicate that fibromyalgia pain varies considerably on a day-to-day basis. No time ($P = 0.09$), group ($P = 0.55$) or interaction ($P = 0.57$) effects were observed on FIQ pain scores in weeks 1 to 8 following treatment (Figure 6). The number of responders as assessed from the FIQ pain score did not differ between treatments and averaged to 2 patients irrespective of treatment (Figure 3).

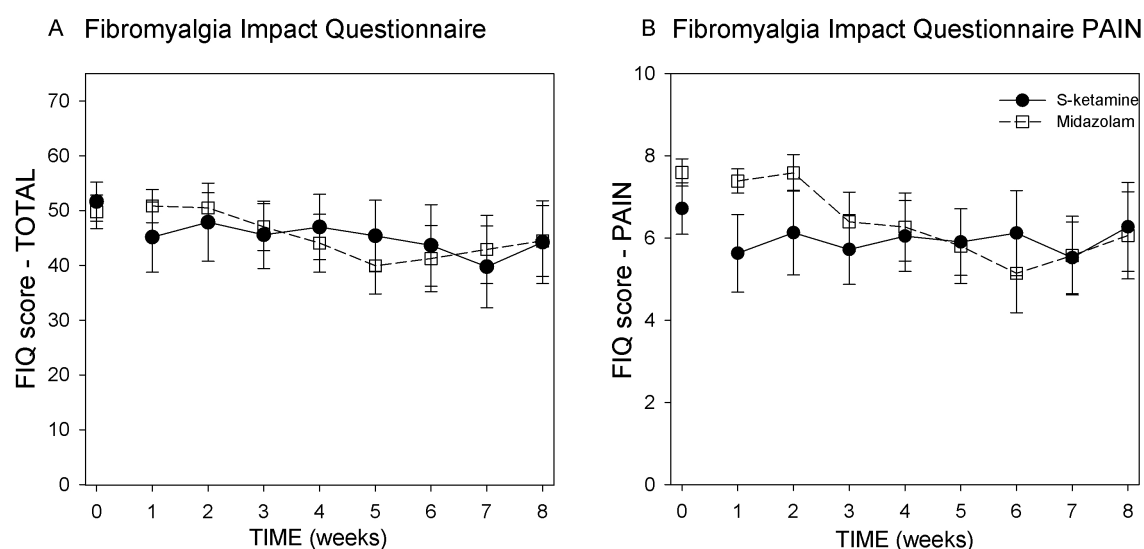


Figure 6 Effect of S-ketamine (closed circles) or midazolam (open squares) treatment on the Fibromyalgia Impact Questionnaire (FIQ). **A** Total scores. **B** FIQ pain scores. No treatment effect or time effect was observed during the 8-week follow-up period. Data are mean \pm SEM.

Blinding

Seven patients (58 %) receiving ketamine guessed correctly which treatment they received (Cohen's kappa = 0.16). In contrast, 11 of 12 patients receiving midazolam stated the correct treatment (Cohen's kappa = 0.83).

Effect of open-label treatment on the FIQ

The FIQ values observed after open-label treatment with S-ketamine did not differ from that the values observed in the RCT (data not shown).

Discussion

We observed no significant effect from intravenous S-ketamine on spontaneous and experimental pain-parameters in fibromyalgia patients in the hours and 8 weeks following a 30-min intravenous treatment with 0.5 mg/kg compared to an

active placebo (5 mg midazolam). A small effect cannot be ruled out in the initial 45-min following treatment when taking into account the number of responders (eight responders in the S-ketamine group versus three in the midazolam group). Overall the efficacy of a 30 min infusion of S-ketamine in the relief of pain in fibromyalgia patients is disappointing despite the relatively large dose given. The effect of S-ketamine on fibromyalgia and experimental pain closely followed the measured plasma concentrations, indicating that the effect that was observed was driven by ketamine's pharmacokinetics.

Comparison with the literature

There are two previous RCTs on the efficacy of ketamine in fibromyalgia patients. Sørensen et al. studied the effect of 0.3 mg/kg racemic ketamine given intravenously over 30 min in 16 fibromyalgia patients and observed reduction in pain scores > 50% in 8 patients during treatment.¹⁷ Four of the responders had a significant improvement of FIQ and pain scores (> 50% of baseline) for 1 to 5 days following treatment. Long-term follow-up (> 7 days) was not performed. The authors conclude that they cannot exclude a possible placebo effect. Graven-Nielsen et al. used a similar infusion regimen (0.3 mg/kg racemic ketamine given over 30 min) in 15 fibromyalgia patients (these 15 patients were responders to ketamine as tested in a previous assessment). They observed a significant analgesic effect during and up-to 150 min following treatment relative to placebo.¹⁸ The results of these two studies are similar to ours, indicating a limited analgesic effect of ketamine in fibromyalgia patients after a single or short-term (30 min) infusion irrespective of dose.

Of interest is further the finding that a positive response to intravenous ketamine (dose around 0.1 mg/kg) in fibromyalgia patients may be used as predictive tool in treatment of pain with either oral ketamine or oral dextromethorphan.^{6,7,19} These data indicate the usefulness of intravenous infusion tests with ketamine in the selection of chronic pain patients for long-term treatment with NMDAR antagonists. See for a critical review of the various intravenous infusion tests tool for prediction long-term treatment effect Cohen et al.²⁰ The observation that 8 of 12 of our patients had pain relief > 50% at $t = 45$ min suggests that these patients could respond in the long-term to either oral ketamine or oral dextromethorphan treatment.^{6,7,19}

Ketamine efficacy in fibromyalgia

We tested an infusion of short duration (30 min) and administered a relatively high dose of S-ketamine (0.5 mg/kg) in that period. We based our study design on earlier observations from our laboratory that short infusions may produce long-term pain relief, i.e., pain relief lasting longer than S-ketamine's pharmacokinetics

predicts. In CRPS-1 patients and small-fiber neuropathy patients (Niesters, unpublished observations) pain relief lasting > 24 h is observed after a short infusion with 0.5 mg/kg S-ketamine.¹⁰ Similar observations are made in animal models of neuropathic pain.⁹ Furthermore, patients with therapy-resistant depression display long-term relief of symptoms following a single 0.5 mg/kg infusion with racemic ketamine.¹¹ All of these effects are thought to arise from a cascade of molecular changes at spinal and supraspinal sites that was initiated by blockade of the NMDAR by ketamine.^{5,9,10,14,16,21,22} Our lack of effect of ketamine treatment may indicate the need for continuous ketamine infusions to obtain long-term analgesic benefit in fibromyalgia patients. For example, Amr, Sigtermans et al. and Schwartzman et al. performed RCTs on the efficacy of long-term ketamine administration (4 -14 days) in neuropathic pain patients from spinal cord injury and CRPS-1 and observed long-term pain relief (weeks to months).^{14,16,23,24} This suggests that long-term ketamine exposure to affected spinal and supraspinal areas is required to cause long-term analgesia (due to a “reboot” of the affected central nervous system).²⁵ Alternatively, it may be that subpopulations of fibromyalgia patients have symptoms potentially not mediated via sensitized NMDAR. Guedj et al. found distinct brain functional SPECT patterns in responders versus non-responders to subsequent ketamine treatment in fibromyalgia patients.^{26,27} Furthermore, the change in the midbrain regional cerebral blood flow after ketamine was highly correlated with the reduction in VAS pain scores during treatment.²⁷ A possible heterogeneity of pathophysiological profiles in fibromyalgia patients may have influenced the outcome of our study.²⁸

Critical review of the protocol

Taken our negative and opposing stand regarding the efficacy of ketamine in the treatment of fibromyalgia pain a critical review of our protocol is needed. We choose an S-ketamine dose of 0.5 mg/kg. Since the S(+)-enantiomer of ketamine is about twice as potent as racemic ketamine our dose compares to 1.0 mg/kg racemic ketamine.⁸ This dose is 2.5 times higher than used in the studies of Sörensen et al. and Graven-Nielsen et al.^{17,18} We expected that the use of this relatively high dose would result in a long-term analgesic effect, at least longer than observed by Sörensen et al. and Graven-Nielsen et al. Our current results contradict this and suggest that it is not the dose but the duration of infusion that is the critical factor in producing pain relief.

In contrast to Sörensen et al. and Graven-Nielsen et al., we compared our treatment to an active placebo, the benzodiazepine midazolam.^{17,18} It may well be that compared to an inactive placebo (such as normal saline) our results would have been more favorable towards an analgesic effect of S-ketamine. We choose this active placebo to induce a similar level of sedation and a similar occurrence of

psychotomimetic side effects during treatment. We did succeed in that during the 30-min infusion period, most subjects, irrespective of treatment, were sedated and unable to retain their consciousness for a sufficient extent of time to respond to questions. Following treatment side effects were mild to moderate in both study groups (see for an example of side effects drug high and drowsy Figure 5) and declined rapidly. Some (5 out of 13 tested) psychotomimetic side effects were greater in patients receiving S-ketamine at time point $t = 45$ min only. The occurrence of sedation during treatment together with the use of an active control adequately masked treatment allocation during the measurement period in our study. Consequently, the absence of a treatment difference is unrelated to a possible difference in side effect profile between the two treatment drugs. Furthermore the patients in the ketamine group were adequately blinded as just 58% of patients were correct in stating which treatment they received (Cohen's $\kappa = 0.16$).

The active placebo that we used, the benzodiazepine midazolam, causes some muscle relaxation and anxiolysis. This may have affected the results of our study. Indeed pain relief from midazolam was observed at $t = 45$ and 180 min, however, the effects were small (a reduction by 1.5 cm only). This suggests just a small effect of muscle relaxation and anxiolysis on the study outcome. Still, the use of the active placebo may have reduced the contrast between treatments. We do argue, however, that by using midazolam we controlled for the sedation and other ketamine side effects without causing large effects on pain relief, as *a priori* intended.

Due to the occurrence of severe sedation during the 30-min S-ketamine and midazolam infusion, we were unable to obtain pain scores during treatment and during the initial part of the recovery period (i.e., $t < 45$ min). Because of this approach we may have missed a possible significant difference in pain scores between treatments. Indeed, Sørensen et al. and Graven-Nielsen et al. show large reductions in pain scores to values < 1 (on a scale from 0 to 10) at the end of their 30-min treatment period.^{17,18} The lack of significant differences between ketamine and midazolam groups in the hours following treatment does indicate that our study was underpowered. A post hoc power analysis revealed that 30 patients per treatment group were required to observe a significant effect in the 3 hours following treatment.

In summary, we reject the hypothesis that a short-term infusion of relatively high-dose S-ketamine treatment produces long-term pain relief in fibromyalgia patients. Possibly, long-term analgesic effect is feasible with more prolonged or repetitive intravenous infusion regimens or daily treatment with oral ketamine or oral dextromethorphan.

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