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Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study

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Abstract

Few placebo-controlled trials have investigated the treatment of breakthrough pain (BTP) in patients with chronic pain. We evaluated the efficacy and safety of intranasal ketamine for BTP in a randomized, double-blind, placebo-controlled, crossover trial. Twenty patients with chronic pain and at least two spontaneous BTP episodes daily self-administered up to five doses of intranasal ketamine or placebo at the onset of a spontaneous BTP episode (pain intensity ≥ 5 on a 0–10 scale). Two BTP episodes at least 48 h apart were treated with either ketamine or placebo. Patients reported significantly lower BTP intensity following intranasal ketamine than after placebo ($P < 0.0001$), with pain relief within 10 min of dosing and lasting for up to 60 min. No patient in the ketamine group required his/her usual rescue medication to treat the BTP episode, while seven out of 20 (35%) patients in placebo group did ($P = 0.0135$). Intranasal ketamine was well tolerated with no serious adverse events. After ketamine administration, four patients reported a transient change in taste, one patient reported rhinorrhea, one patient reported nasal passage irritation, and two patients experienced transient elevation in blood pressure. A side effect questionnaire administered 60 min and 24 h after drug or placebo administration elicited no reports of auditory or visual hallucinations. These data suggest that intranasal administration of ketamine provides rapid, safe and effective relief for BTP.

Keywords: Ketamine; Intranasal; Pain; Chronic; Breakthrough; Randomized controlled trial

1. Introduction

Breakthrough pain (BTP) is a flare-up of moderate-to-severe pain, that 'breaks through' despite a by-the-clock analgesic regimen for treatment of chronic pain (Mercadante and Arcuri, 1998; Portenoy and Hagen, 1990). BTP is by definition severe and has a significant impact on a patient's quality of life (Mercadante and Arcuri, 1998; Portenoy and Hagen, 1990). This estimate of prevalence of BTP implies that more than 800,000 cancer patients in the US alone suffer from BTP (Carr et al., 2002; Goudas et al., 2001; Mercadante and Arcuri, 1998). A recent systematic review of randomized controlled trials of cancer pain management found only two such trials investigating BTP treatment; both evaluated oral transmucosal fentanyl citrate (Carr et al., 2002; Goudas et al., 2001; Farrar et al., 1998; Portenoy et al., 1999).

Although BTP is typically treated with opioids, patients chronically receiving opioids may display progressive tolerance, and so the use of non-opioid agents to treat

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BTP on a long-term basis is an attractive concept. Ketamine is a widely used anesthetic agent administered intravenously, intramuscularly, orally, rectally, intranasally or spinally, alone or in combination with opioids (Chia et al., 1998; Gehling and Tryba, 1998; Malinovsky et al., 1996; Mercadante et al., 2000; Walker et al., 2002). The safety and efficacy of ketamine as an anesthetic and analgesic agent is well documented (Malinovsky et al., 1996; Reich and Silvay, 1989; White et al., 1982). One case study suggests the feasibility of the nasal route of administration of ketamine (Kulbe, 1998). Ketamine is not labeled by the FDA as an analgesic agent. However, low doses of ketamine (administered intranasally or otherwise) have been used as an anesthetic pre-medication (Kohrs and Durieux, 1998; McCarty et al., 1999) and as treatments for neuropathic pain (Eide et al., 1994, 1995; Jackson et al., 2001; Kannan et al., 2002; Klepstad and Borchgrevink, 1997; Mercadante et al., 1995, 2000; Mercadante and Arcuri, 1998), phantom limb pain (Knox et al., 1995), post-operative and other post-traumatic pain (Dich-Nielsen et al., 1992; Gurnani et al., 1996; Hirlinger and Dick, 1984; Hirlinger and Pfenninger, 1987; Lauretti and Azevedo, 1996; Owen et al., 1987); and to control pain during burn dressing changes (Bookwalter, 1994; Humphries et al., 1997; Kulbe, 1998; Pal et al., 1997). Low (analgesic) doses of ketamine have minimal adverse impact upon cardiovascular or respiratory function (Miller et al., 2000).

The large surface area, uniform temperature, high permeability and extensive vascularity of the nasal mucosa (Chien et al., 1989), and its ease of access facilitate rapid systemic absorption of intranasally administered drugs such as opioids (Dale et al., 2002). Additionally, intranasal delivery represents a needle-free, patient-friendly route of administration in contrast to painful intramuscular injections and/or intravenous delivery (Wermeling et al., 2002).

The present randomized, double-blind, placebo-controlled, two-period crossover trial aimed to evaluate the safety and the efficacy of 1–5 sprays (10–50 mg total) of intranasal ketamine to treat BTP in patients with chronic pain.

2. Methods

2.1. Study protocol and consenting procedures

The study protocol design was a two-period crossover trial where each patient was randomized to receive one of two possible treatment sequences (ketamine followed by placebo versus placebo followed by ketamine). The experimental protocol, informed consent form and advertisements for this study were reviewed and approved by the Human Investigational Review Boards (HIRBs) of the Tufts-New England Medical Center, the Methodist Comprehensive Pain Institute, and the Johns Hopkins Hospital. All participating patients were provided with oral and written information describing the nature and duration of the study and provided informed consent. Patients first visited one of the three study centers in order to be screened (visit 1). At least 7 days but no more than 2 weeks after this visit, they visited the study center again on two additional occasions (visits 2 and 3) at least 48 h apart, once to be tested with intranasal ketamine hydrochloride and once to be tested with placebo. Study procedures are schematically summarized in Fig. 1. The study was conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the South Africa revision (1996) (World Medical Association, 1964).

2.2. Patient recruitment and inclusion/exclusion criteria

Study subjects were recruited by advertising in local newspapers and by referrals from the pain clinics of the three sites. Inclusion criteria for enrollment were: (a) age 18 years or older; (b) a stable pattern (i.e. for the 2 weeks prior to enrollment) of 2–7 episodes of daily BTP despite taking stable by-the-clock doses of analgesic medication; (c) ability to communicate the intensity of pain using a numerical pain intensity scale; (d) willingness to maintain a daily diary of BTP episodes for 7 days immediately prior to the first of the two testing days (i.e. visit 2); (e) spontaneous BTP episodes on the days of testing (i.e. visits 2 and 3) of intensity ≥ 5 on the numerical pain intensity scale (NPIS) prior to administration of study medication or rescue medication for BTP; (f) demonstration of ability to properly use the nasal spray pump prior to enrollment; and (g) ability to understand and cooperate with study procedures. The by-the-clock medication was equivalent to at least 60 mg/day of morphine in a controlled release preparation (e.g. MS-Contin, OxyContin or Duragesic). The medication for relief of BTP should be equivalent to at least 5 mg immediate release morphine or its equivalent as a short-acting opioid (e.g. oxycodone, hydrocodone, or codeine with acetaminophen).

Patients were excluded from the study if they: (a) had a history of intolerance, hypersensitivity, or known allergy to ketamine; (b) had a new analgesic(s) added to their analgesic regimen within 2 weeks prior to the trial; (c) were taking potentially interfering medications (e.g. dextromethorphan); (d) had nasal/sinus anomalies or dysfunction (e.g. allergic or infectious rhinitis); (e) were experiencing an acute illness or other medical event that might potentially alter their numeric pain intensity scale (NPIS) ratings; (f) had cognitive impairment objectively documented or in an investigator's judgment, or who were experiencing a life crisis or other emotional event that would be expected to alter their pain intensity or responsivity; (g) were pregnant women, nursing mothers and women of childbearing potential not using contraception known to be reasonably effective; (h) had participated in an investigational drug or device trial during 1 month prior to study entry or during the course of

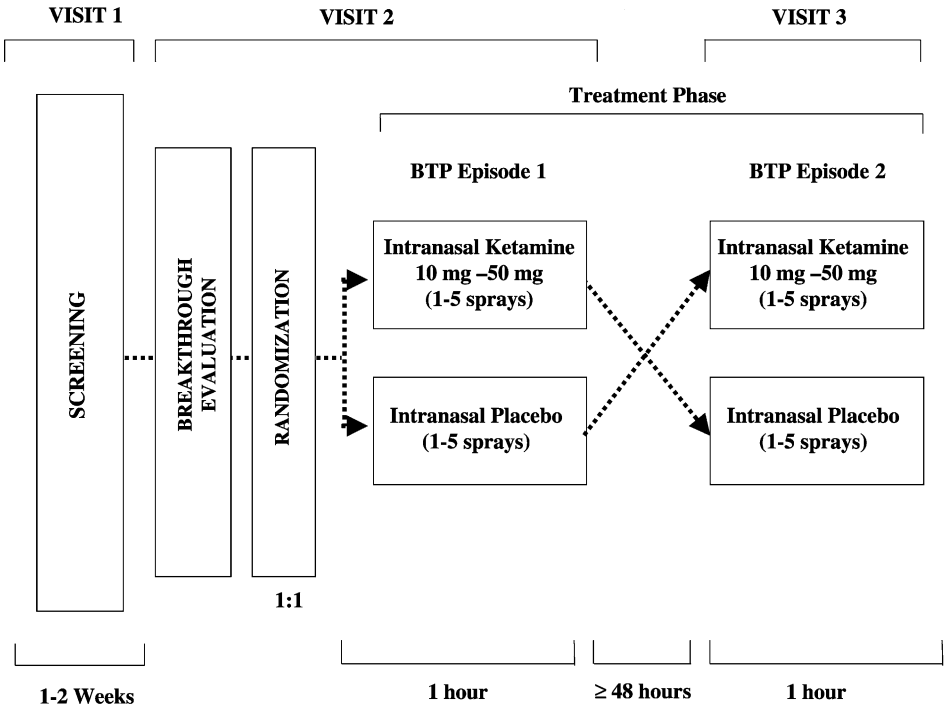


Fig. 1. Schematic representation of the study design.

the study; (i) had a known history of significant cardiac, hepatic, lung, or psychiatric disorder; (j) were unable to understand written and verbal English; (k) had a history of cardiac events including arrythmias, congestive heart failure, or angina, or who were considered to fall in class III or IV of cardiac risk according to the New York Heart Association (NYHA) classification system; (l) had poorly controlled hypertension (systolic BP >180 mmHg or diastolic BP >90 mmHg despite antihypertensive therapy), or who had a history of hypertensive crisis(es) at any time in the past; (m) had a history of transient ischemic attacks, neural vascular disease, stroke, or cerebral aneurysms; and (n) weight less than 50 kg.

2.3. Randomization, blinding and concealment procedures

The patients, investigators, and sponsor were blinded to the study therapy until all patients completed the protocol and the study ended. Randomization was performed using a random number table provided by an independent statistician. A table in which a '0' or a '1' were assigned to the numbers from 1 to 20 was provided directly to the clinical trial pharmacist. Upon arrival of each subject for the first session, either placebo (for a 0) or ketamine hydrochloride (for a 1) was dispensed by the pharmacist according to the number corresponding to that patient's entry in the accrual sequence. The pharmacist kept a record of subject numbers and treatment given (study code). The treatment given at visit 3 was the alternative to that given at visit 2. The study code was available to the investigators immediately upon request in case of adverse reactions.

The research pharmacies of the participating centers prepared and supplied the ketamine and the placebo (vehicle only, see below) preparations in 20 ml Type II amber glass bottles capped with a metered dose spray applicator (VP7/100, Valois, Congers, NY). Masking was assured by identical packaging of active drug and placebo. The identity of the test preparation was concealed on the masked portion of the label.

2.4. Drug formulation and test drug administration procedures

The study drug was formulated as a 10% aqueous solution of ketamine hydrochloride with 0.002% benzalkonium chloride (vehicle) in a nasal spray pump. The study drug was prepared to be applied intranasally using a 0.1 ml metered nasal spray pump attached to a 20 ml reservoir bottle. Each spray delivered a total of 10 mg of ketamine hydrochloride. Patients who met inclusion criteria and provided informed consent were admitted into the outpatient research clinics of the participating institutions. Once there, and immediately upon their report that a BTP episode was starting, they self-administered one spray nasally up to a maximum of five separate sprays in alternate nostrils until satisfactory analgesia was achieved. All enrolled patients administered the drug under close supervision of study staff to ensure safe titration. The interval between successive sprays was 90 s. All patients were instructed that if they did not receive adequate pain relief after five sprays or 7.5 min from the first nasal drug administration, they should take a dose of their usual BTP

medication. The maximum total dose of ketamine hydrochloride was 50 mg.

2.5. Study procedures and outcomes

2.5.1. Sample size determination

The sample size of 20 patients was based on the ability to detect a 0.57 standardized difference (mean difference between treatments divided by the SD of the paired difference) with 80% power for a one-sided hypothesis test with 5% Type I error using the pain intensity on the NPIS for each treatment under study. A one-sided test was deemed to be appropriate given the longstanding history of ketamine as analgesic.

2.5.2. Screening

Following initial telephone communication and interview each patient visited the study center (visit 1) 1–2 weeks prior to initial treatment (visit 2) and crossover treatment (visit 3). During visit 1, prospective patients underwent a physical examination that included a sensory examination to assess neuropathic pain, and were asked to record on an NPIS the intensity of pain experienced during a typical episode of BTP when using their current method of BTP relief. Females provided a urine sample for pregnancy testing. At this point patients read and signed the informed consent form in the presence of one of the investigators. They then were instructed to keep a diary of BTP episodes as well as their intake of analgesics and other medication for seven consecutive days immediately prior to visit 2. Patients were also instructed on the use of the spray container. Subjects were informed that they could withdraw from the study at any time without adverse effect upon their normal clinical care. Subjects were discontinued from the study if, in the opinion of the investigators, doing so was warranted as a result of an adverse event.

2.5.3. Study drug testing

Visits 2 and 3 started with the investigators reviewing the pain diary and repeating the sensory examination. After ensuring that each patient still satisfied inclusion criteria, monitoring of vital signs began. Monitoring included continuous measurement of arterial oxygen saturation (SaO_2) by pulse oximetry, non-invasive arterial blood pressure and heart rate. Monitoring continued throughout the remainder of the visit. An indwelling 'saline lock' intravenous catheter was inserted in each subject and a 10 ml blood sample was drawn for a complete blood count, PT/PTT, and serum chemistries, including ketamine, creatinine, glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, uric acid, phosphorus, calcium, total protein, albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, total bilirubin, and lactose dehydrogenase. Additional 10 ml samples were drawn, and replaced with 10 ml of saline, at 2, 30 and 60 min after the last nasal dose of ketamine hydrochloride or placebo at each visit. The catheter was then removed and an occlusive dressing was applied to the catheter entry site. A nasal examination was performed to examine the integrity of the nasal mucosa before treatment at visits 2 and 3.

After admission to the study ward, and baseline vital sign monitoring and blood sampling, each patient then rested until a BTP episode developed. Pain intensity assessed on the NPIS was recorded at the onset of BTP. If the NPIS intensity was ≥ 5, the patient was given a coded container with ketamine or placebo and advised to self-administer 1–5 single sprays at intervals of 90 s using alternate nostrils. The NPIS recording was repeated at 5, 10, 15, 20, 25, 30, 40, 50 and 60 min after the first spray of study medication. If pain relief was achieved with fewer than five sprays, patients did not self-administer additional sprays. All patients were instructed to take their allowed dose of usual rescue medication if they did not achieve pain relief within five sprays or 7.5 min of the initial spray of ketamine or placebo. If the pain rating on the initial NPIS was less than five, the patient was advised to wait for another breakthrough episode before taking the study medication. If a patient had used his/her rescue medication on the day of visit 2 or 3 at any time prior to the study drug administration, they were not permitted to continue testing on that day. Subject evaluation after treatment included a physical examination, a nasal exam, EKG, and serum chemistries as described above. The investigator reviewed the NPIS ratings with the patient and administered the side effects rating scale for dissociative anesthetics (SERSDA) (see Appendix A), documented any adverse events reported by the patient, and made a global assessment of response to the study drug rating it as 'good', 'fair', or 'poor'. The side effects scale was administered immediately after the final NPIS rating (approximately 60 min after the first administration of study medication). Patients remained at each study site for observation for at least 3 h, or longer if deemed clinically necessary. A follow-up phone call was placed 24 h after administration of drug following both visits 2 and 3 to assess possible adverse events utilizing the SERSDA.

2.6. Determination of plasma ketamine and norketamine concentrations

Blood samples collected in heparinized 2, 30, and 60 min after the administration of the final dose were kept frozen ($-20\,^{\circ}C$) until analysis. Samples were analyzed for ketamine and norketamine according to a validated bioanalytical method that was developed internally by PPD Development (Middleton, WI). The limits of this method to quantitate ketamine and norketamine fall within a nominal range of 0.500–500 ng/ml. Two-hundred microliter sample aliquots were fortified with 25 μl of internal standard solution. All samples were then subjected to liquid–liquid extraction with hexane and then re-extracted with 300 μl formic acid and the supernatant was aspirated. Twenty microliters of the final extract were injected and

analyzed via HPLC (Series 1100, Hewlett Packard GmbH, Waldbronn, Germany) with mass spectrometry (Quattro Ultima, Micromass UK Limited, Manchester, UK). Linearity was indicated by an average correlation coefficient from three standard curves of 0.9999 for ketamine and 0.9998 for norketamine over a concentration range of 0.500–500 ng/μl. Inter-assay precision and accuracy of the HPLC assay for ketamine were determined by assaying samples with four known concentrations of ketamine at different times. These concentrations were 0.5, 1.5, 15.0 and 375 ng/ml. Assay precision (coefficient of variation, CV, $<1\%$) and accuracy (CV $<3\%$) were deemed acceptable.

2.7. Data recording and statistical analyses

Data for each patient were prospectively recorded on a case report form (CRF). Analyses followed a pre-approved analysis plan that specified study populations, analysis methods, and significance testing.

The intent-to-treat (ITT) population consisted of all patients who were randomized and who received both the initial and crossover treatments and had the follow-up efficacy data collected.

The patient population at baseline was assessed for balance in terms of the following covariates: treatment order, age, sex, race, disease type, medical history, previous systemic conditions such as diabetes or vascular disease, smoking history, alcohol or drug intake, and chemical exposure at work, as well as baseline NPIS pain at breakthrough. The percentages of patients who were ineligible, who withdrew prior to the crossover phase, who took medications that violated the protocol or who violated the protocol for any reason were recorded.

The primary efficacy analysis consisted of a two-stage crossover analysis of a summary measure of change in NPIS score. A 40% reduction in NPIS scores from baseline was considered a meaningful reduction in pain intensity (Cepeda et al., 2003; Farrar, 2000, 2001). The nine NPIS scores recorded after the onset of the BTP episode were compared to the initial NPIS score at the onset of the episode using the Friedman Repeated Measures ANOVA on Ranks test. The summary measure of changes in NPIS scores was calculated by averaging the nine post-treatment NPIS measurements, and then subtracting the baseline NPIS measurement. Rank tests with exact critical values were performed to evaluate differential carryover effect, period effect, and treatment effect. Subjects who received both the placebo and the active treatment were used in this analysis. A Wilcoxon signed rank test was used to compare paired NPIS scores at each post-baseline time. In addition, 95% confidence intervals were drawn for each treatment at each time point. All statistical tests of significance for efficacy were one-sided and were considered statistically significant ($P < 0.05$) or marginal ($P < 0.10$). No correction for multiple testing was required since a single primary endpoint of NPIS was pre-specified.

The incidence of adverse events by time of occurrence, severity, and relationship to the treatment (ketamine or placebo) as judged by the investigator were displayed for each treatment group.

No interim analyses were performed. SAS (Version 6.12, Cary, NC) was used for all statistical analyses.

3. Results

3.1. Demographic and baseline data

A total of 22 patients were randomized for this study. The first patient entered the study on 17 May 2000 and the last patient completed visit 3 on 15 August 2001, with a follow-up phone call on 16 August 2001. Each clinical trial site used its own laboratory (all accredited by The College of American Pathologists) for all screening blood tests. Two patients who were randomized to enter the placebo/ketamine arm of the study did not receive any study medication. One patient withdrew consent and another was not able to have a catheter inserted for blood sampling. Twenty patients (10 randomized to the ketamine/placebo arm and 10 randomized to the placebo/ketamine arm) completed the study and received study medication at both visits 2 and 3.

Demographic characteristics for the safety population are presented in Table 1. Each treatment arm was comprised of three males and seven females. Nineteen out of 20 patients were Caucasian, with one Hispanic patient only in the placebo/ketamine group.

Enrolled patients suffered from a variety of chronic, painful conditions. Thirteen of the 20 patients who received study medication cited some degree of back pain. Four patients listed fibromyalgia in their medical history. Four patients had a history of some form of cancer, including metastatic lung cancer (one patient), breast cancer (one patient), bladder cancer (one patient), and cervical cancer (one patient). Other painful conditions included, but were not limited to sinus pain (one patient), reflex sympathetic dystrophy (one patient), chronic vaginal pain and rectal pain (one patient), Lyme disease (one patient), osteoarthritis (one patient) and rheumatoid arthritis (two patients).

3.2. Concomitant medications

Each of the 20 patients who received study medication had used opioids for at least 6 weeks prior to visit 2. Opioids used previously and/or currently included oxycodone, morphine sulfate, methadone, fentanyl, hydrocodone, and hydromorphone. Other medications used for pain included but were not limited to, amitriptyline, gabapentin, nabumetone, methocarbamol, clonazepam, temazepam, celecoxib, rofecoxib, tramadol, ketorolac, and aspirin. Concomitant medications were used by patients for indications other than pain including allergies, hormone replacement therapy,

Table 1
Demographic and other baseline data-safety population

	Ketamine/placebo ($N = 10$)	Placebo/ketamine ($N = 10$)
Sex [N (%)]		
Male	3 (30)	3 (30)
Female	7 (70)	7 (70)
Missing	0 (0)	0 (0)
Age		
N	10	10
Mean (SD)	53.10 (14.279)	44.0 (12.02)
Median	51.0	43.5
Min–max	28.0, 70.0	23.0, 68.0
Weight (kg)		
N	10	10
Mean (SD)	74.12 (22.363)	84.56 (21.767)
Median	70.5	74.8
Min–max	46.0, 118.0	65.0, 123.0
Smoking [N (%)]		
Yes	4 (40)	3 (30)
No	6 (60)	7 (70)
Missing	0 (0)	0 (0)
Current alcohol use [N (%)]		
Yes	4 (40)	3 (30)
No	6 (60)	7 (70)
Missing	0 (0)	0 (0)
Current drug use [N (%)]		
Yes	1 (10)	0 (0)
No	9 (90)	10 (83)
Missing	0 (0)	0 (0)
Exposed to chemicals at work [N (%)]		
Yes	0 (0)	1 (8)
No	10 (100)	9 (75)
Missing	0 (0)	0 (0)
Visit 1 NPIS score		
N	10	10
Mean (SD)	6.00 (2.357)	7.6 (0.966)
Median	6.0	7.5
Min–max	1.0, 10.0	6.0, 9.0

thyroid conditions, non-insulin dependent diabetes, elevated cholesterol, depression, hypertension, respiratory disorders, and insomnia.

3.3. Protocol deviations

Five patients were noted to have protocol deviations during the study. None were excluded from any analysis populations due to these deviations. Examples of protocol deviations occurring during the study were: one patient who was only able to administer study medication through one nostril at visit 2 due to an abrasion, and another patient, who initiated new analgesic medications (celecoxib and transdermal fentanyl) within 2 weeks prior to participation in the clinical study.

3.4. Pain outcomes

The primary endpoint of the study was the mean NPIS score following intranasal administration of ketamine and placebo compared to baseline, and the primary goal was to compare the mean reduction of NPIS score between treatment with ketamine and placebo using the modified ITT population. As no statistically significant period or carryover effects were demonstrated in the modified ITT population, the changes from the pre-treatment NPIS scores according to ketamine or placebo were evaluated for aggregated visits 2 and 3 data. The aggregated changes from pre-treatment scores, as well as the average of the pre-treatment scores and the average of the post-treatment scores for visits 2 and 3, are presented for ketamine and placebo in Table 2. The primary efficacy endpoint was confirmed using the NPIS area under the curve for the first 60 min following treatment administration. The mean reduction in NPIS score for the ketamine-treated group was 2.65 units while the mean reduction for the placebo-treated group was 0.81 units ($P < 0.0001$, Wilcoxon signed rank test). Declines from pre-treatment NPIS scores following treatment were 2.82 in the ketamine group versus 1.11 in the placebo group at visit 2 and 2.47 in the ketamine group versus 0.51 in the placebo group at visit 3.

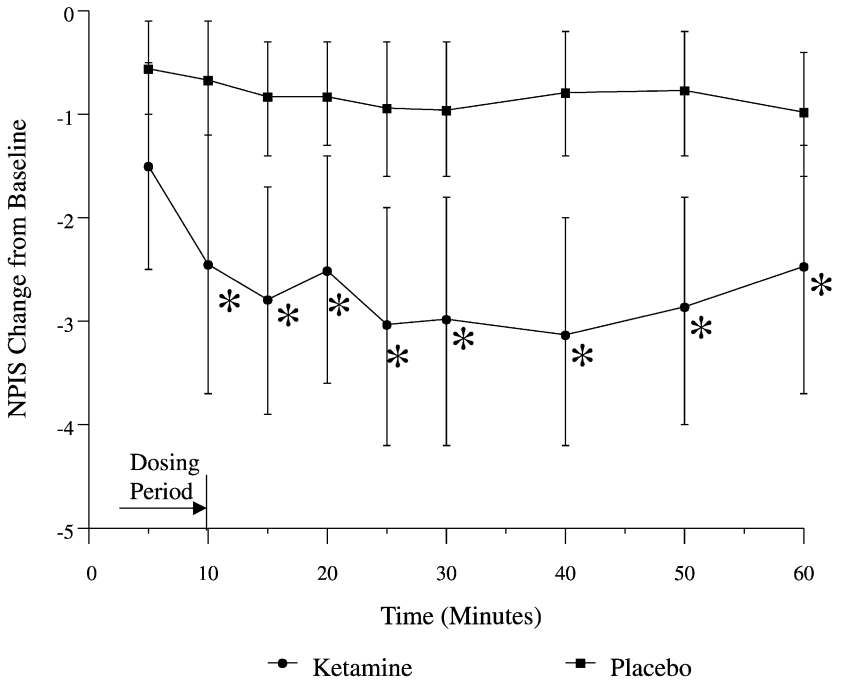
The relative therapeutic benefit of ketamine versus placebo was confirmed in the ITT population by a general estimating equation (GEE) analysis with factors of treatment, period and carry-over that used both visits 2 and 3 data. This analysis demonstrated a statistically significant treatment effect ($P = 0.0007$) with no evidence of a carryover effect ($P = 0.8206$) or period effect ($P = 0.1858$). The time course of NPIS scores following treatment with both ketamine and placebo is displayed graphically in Fig. 2.

After treatment with ketamine, 13 of 20 (65%) patients achieved a minimum NPIS score that was at

Table 2
Evaluation of treatment effect

	Ketamine ($N = 20$)	Placebo ($N = 20$)	*P*-value[a]
Reduction in NPIS			<0.0001
N	20	20	
Mean (SD)	−2.65 (1.87)	−0.81 (1.01)	
Median	−2.3	−0.2	
Visit 2 N	10	10	
Pre-treatment NPIS, mean (SD)	7.21 (1.76)	7.46 (1.31)	
Average post-treatment, NPIS, mean (SD)	4.39 (2.26)	6.35 (2.03)	
Visit 3 N	10	10	
Pre-treatment NPIS, mean (SD)	6.92 (1.13)	7.20 (1.45)	
Average post-treatment NPIS, mean (SD)	4.45 (2.35)	6.69 (1.99)	

[a] Wilcoxon signed rank test.



Collection Time	2 min	30 min	60 min
Ketamine [ng/mL]	22.4 ± 16.8	49.8 ± 29.8	39.9 ± 20.6
Norketamine [ng/mL]	0.06 ± 0.22	45.5 ± 34.1	66.1 ± 30.6

Fig. 2. Aggregate NPIS score changes from baseline over time in the placebo and ketamine groups. Changes from baseline are expressed as averages with 95% CI error bars. Data points with asterisks(*) are statistically significant compared to placebo. Paired differences were computed at each time point (20 possible pairs). A Wilcoxon sign rank test was used to test for pairwise differences at each time point. The 95% confidence intervals drawn for each treatment were computed using separate one-sample *t*-tests. Also listed are the values (mean ± SD) for plasma concentrations of ketamine and norketamine at 2, 30 and 60 min for the 15 patients who received the full 50 mg intranasal dose of ketamine.

least 40% lower than the pre-treatment score, compared with only four of 20 (20%) in the placebo group. Nine of 20 patients (45%) achieved a mean reduction in NPIS score of $>40\%$ compared to one of 20 patients (5%) following treatment with placebo ($P = 0.0078$). The clinical significance of this effect is further demonstrated by the observation that 14 of 20 (70%) achieved a NPIS score of 4 or less following treatment with intranasal ketamine. Eleven of 20 (55%) patients given ketamine attained a minimum NPIS score of 2.2 or less while an equivalent reduction in NPIS score was achieved in only in two of 20 (10%) patients after treatment with placebo. In contrast, after placebo, 10 of 20 (50%) patients reported no reduction in NPIS score during the BTP episode while only one patient reported no relief after treatment with ketamine.

Statistically significant pain relief occurred within 10 min of the delivery of the final intranasal spray of ketamine and the significant difference compared to placebo persisted for the remaining 50 min of NPIS measurements (Table 3 and Fig. 2). Following treatment with ketamine, 15 of 20 patients (75%) achieved their minimum NPIS within 25 min of administration and eight achieved their minimum NPIS score within 5–10 min.

Table 3
Aggregate NPIS score changes from baseline over time in the placebo and ketamine groups

	Time after start of administration of study drug (minutes)[a]								
	5	10	15	20	25	30	40	50	60
Ketamine	−1.50	−2.45	−2.79	−2.51	−3.03	−2.98	−3.13	−2.86	−2.47
Placebo	−0.56	−0.67	−0.83	−0.83	−0.94	−0.96	−0.79	−0.77	−0.98
P-value[b]	0.2114	0.0039	0.0007	0.0010	0.0003	0.0007	0.0001	0.0001	0.0037

[a] Titration of ketamine may not have been complete until 6 min after start of dosing.
[b] Wilcoxon signed rank test comparing the paired change between treatment groups at each post-baseline time.

3.5. Blood concentrations of ketamine

Blood concentrations of ketamine were measured at 2, 30 and 60 min after initiation of drug treatment. The mean concentration of ketamine was highest at 30 min, which corresponded to the interval of greatest decrease in the NPIS score in ketamine-treated patients. Although the observed mean concentration of ketamine was greatest at 30 min, plasma levels of ketamine were detectable by 2 min after the first spray. At the last observed time point, 60 min, mean ketamine levels had decreased by approximately 20% from peak. Thus, reductions in pain intensity correspond well with blood levels of ketamine (Fig. 2).

3.6. Safety outcomes

All 20 patients who received study medication received both ketamine and placebo and completed both of their visits for BTP treatment and evaluation. There were no patient drop-outs, serious adverse events, or deaths during this study.

Eleven of 20 patients reported side effects on the SERSDA. Ten of 20 (50%) reported side effects following treatment with ketamine and two of 20 (10%) following treatment with placebo. The most commonly reported side effects were fatigue (seven patients post-evaluation, two patients 24-h post-evaluation), dizziness (four patients), feeling of unreality (four patients), changes in vision (two patients), nausea (one patient post-valuation and one patient 24-h post-evaluation). Single incidences of changes in hearing, mood change and generalized discomfort were reported by one patient. More than half of the reported side effects were mild or moderate in severity, and transient in nature, resolving within 60 min of dose administration. Only the feeling of fatigue following treatment with ketamine was statistically significant compared with placebo ($P = 0.0156$). There were no auditory or visual hallucinations reported by any patients.

According to the specific question that elicited this symptom, a change in taste was variably reported as a nasal symptom during the nasal examination, as an adverse event, or as a comment during the investigator's global assessment. Overall, a change in taste that did not exist pre-treatment was reported following treatment with ketamine in three patients.

One patient experienced very bothersome dizziness and feeling of unreality post-evaluation. The same patient also experienced dizziness and headache during placebo administration. This patient also had a fluctuation of blood pressure, with a pre-episode blood pressure of 142/86 mmHg. Twenty minutes into the BTP episode, the patient's blood pressure rose to 169/88 mmHg. At post-evaluation, the patient's blood pressure was 103/53. No serious adverse events were reported during the study. No clinically significant change occurred in the vital signs nor in arterial oxygen saturation. No abnormal hematology or blood chemistry values of clinical significance were reported that were not attributed to a pre-existing condition.

4. Discussion

This randomized, double-blinded, placebo-controlled multicenter crossover study of the treatment of BTP demonstrated a significant analgesic efficacy of intranasal ketamine in comparison to intranasal placebo for BTP in chronic pain patients. To our knowledge, only two randomized, placebo-controlled trials have been reported to date on the efficacy of medications specifically indicated for the treatment of BTP (Carr et al., 2002; Goudas et al., 2001). These two carefully designed trials demonstrated efficacy of oral transmucosal fentanyl citrate compared to placebo (Farrar et al., 1998; Portenoy et al., 1999).

Ketamine, a phencyclidine derivative, was developed and first tested in healthy human subjects for its anesthetic and analgesic properties in the early 1960s. Domino et al. (1965) found that ketamine in doses of 1.0–2.0 mg/kg produced potent analgesia as evident by the lack of reaction to 'pain-inducing procedures' without loss of consciousness and proposed the phrase 'dissociative anesthetic' to describe the mental state that this agent produced. Repeated administration of ketamine did not appear to induce tolerance to its anesthetic and analgesic effects (Domino et al., 1965). The desirable effects of ketamine are counterbalanced by its hallucinogenic and other psychomimetic effects that were observed at subanesthetic doses in healthy volunteers (Domino et al., 1965; Krystal et al., 1994). Indeed, the major limiting factor for ketamine use is its 'dissociative' or 'hallucinogenic' effects. A review of several randomized controlled trials indicates that the required dose range for analgesia through systemic routes—subcutaneous, intravenous or intramuscular—is between 0.3 and 0.5 mg/kg/h (Gehling and Tryba, 1998). At this dose range 'psychomimetic' side effects from ketamine occur in 20–30% of patients or in 15% of patients when used in combination to morphine (Gehling and Tryba, 1998). Similarly, hallucinations were reported in a randomized trial in four out of 10 patients with cancer after bolus intravenous administration of ketamine 0.25 or 0.50 mg/kg for the treatment of neuropathic pain syndromes (plexopathy or spinal cord compression) (Mercadante et al., 2000). In practice, to minimize the incidence of adverse psychological effects clinicians pre-treat or co-administer a benzodiazepine or other hypnotic agent to patients given ketamine (Hurford et al., 2002). Thus, the lack of severity of most psychological responses to ketamine, and the availability of means to minimize these render ketamine a useful agent for the management of pain.

In recent years, evidence for a lack of tolerance to ketamine's analgesic effect (Klepstad and Borchgrevink, 1997), its interactions with multiple receptors such

as the NMDA receptor (Kohrs and Durieux, 1998) that are involved in nociception, and its minimal depressive effect on respiratory drive and circulation have prompted increased interest in its use for acute or chronic pain. Ketamine has been used widely as an analgesic during dressing changes in burned patients (Pal et al., 1997) and as a sedative and/or anesthetic agent for procedures of short duration (Qureshi et al., 1995). Acute post-operative pain, chronic non-cancer pain, or cancer pain in adult patients have all been treated with intravenous, subcutaneous, intramuscular, oral, and transdermal ketamine (Grant et al., 1981). Oral ketamine was evaluated in a set of 'N of 1' randomized, placebo-controlled trials of patients with chronic neuropathic pain who had responded to 20 mg/day oral ketamine in a 1-week unblinded screening study (Haines and Gaines, 1999). Nine patients who reported having benefit without excessive adverse effect in response to ketamine were randomized to receive blindly oral ketamine or placebo for 1 week on three occasions using an N of 1 trial design. Some evidence of benefit in analgesia was demonstrated for only three of these patients and but this was limited by adverse effects (Haines and Gaines, 1999). Patients in this study had not stopped taking their analgesic or other medication (Haines and Gaines, 1999). A systematic review of spinal analgesic drug combinations supports the efficacy of acute addition of ketamine to epidural morphine in patients with cancer pain (Walker et al., 2002). Indeed, pre-clinical studies in vitro (Hirota et al., 1999) and in vivo (Sarton et al., 2001) suggest an interaction of ketamine with the μ opioid receptor as well as with δ and κ opioid receptors. The clinical implications of these observations remain to be defined.

The intranasal route for ketamine administration has been applied only for pain of dressing changes in a single case study (Kulbe, 1998). In this patient, oxycodone and acetaminophen were ineffective to control pain during burn dressing changes in a 96-year-old woman cared for at home. She tolerated the burn dressing changes after three intranasal sprays of 0.1 ml each, in rapid succession, each containing 5 mg ketamine (15 mg total) (Kulbe, 1998).

In the present study a significant analgesic superiority of ketamine over placebo was evident as early as 10 min after administration of study medication and persisted for 60 min. The proportion of patients who attained a 40% or greater reduction in NPIS was higher with ketamine than with placebo. Apart from pain intensity, the use of their usual rescue medication by these patients was lessened following treatment with ketamine as compared to treatment with placebo. Seven patients perceived sufficient unresolved pain following treatment with placebo that they sought relief with their usual rescue medication, but no patient took rescue medication during the 60-min after ketamine. The safety profile following treatment with ketamine was comparable to that seen with placebo.

The physician's global assessment was 'good' for 18 of 20 (90%) patients following treatment with ketamine while only two were rated 'fair' or 'poor'. It is unlikely that patients would have received an overall assessment of good from the physician if their side effects were causing concern. The difference in the number of side effects reported following treatment with either ketamine or placebo could be expected, as ketamine has been associated with these specific side effects, although at near anesthetic doses. Therefore the difference in the number of side effects between the two treatments probably suggests a greater severity of discomfort than that actually experienced following treatment with ketamine by comparison to placebo. The patients enrolled in our study had previously used one or more opioids and were required to be taking the equivalent of 60 mg/day morphine for chronic pain. Although patients did report side effects of fatigue, dizziness and feelings of unreality more often following treatment with ketamine than following treatment with placebo, no patient reported hallucinations and the side effects were generally reported to be of mild or moderate severity, and transient. No serious adverse events were reported and the incidences of associated adverse events were comparable for ketamine and placebo. Although study medication was administered intranasally, nasal signs and symptoms were few and inconsequential. A distinctive taste, however, was reported more often following treatment with ketamine than following treatment with placebo.

In conclusion this randomized, placebo-controlled, double-blind study, in 20 patients, has demonstrated that intranasal ketamine is safe and effective for BTP. Our findings augment an early but promising literature documenting the effectiveness of nasal administration of a variety of opioids for pain management in adults (Dale et al., 2002) However, large scale clinical investigations of ketamine after repeated intranasal administration in patients with diverse types of chronic pain and/or BTP are warranted. Safety issues relating to ketamine's psychotomimetic effects, its potential to impair cognitive function, to irritate the nasal mucosa, as well as its addictive potential should be extensively investigated before widespread use in clinical practice.

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Appendix A

Side effects rating scale for dissociative anesthetics (Eide et al., 1994)

Side effects	Severity of side effects scale
Fatigue	0, no change
Dizziness	1, weak
Nausea	2, modest
Headache	3, bothersome
Feeling of unreality	4, very bothersome
Changes in hearing	
Changes in vision	
Mood change	
Generalized discomfort	
Hallucination	

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