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Transdermal Ketamine and S(+)-Ketamine as Adjuvants Following Orthopaedic Surgery under Bupivacaine Spinal Anaesthesia

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Abstract

The aim of the study was to examine the perioperative analgesic effect of topical deliver of either ketamine or S(+)-ketamine in orthopaedic postoperative pain through clinical and laboratorial evaluation. 45 patients following minor orthopaedic surgery were randomized to one of three groups (n=15). Spinal anaesthesia was performed with 15 mg hyperbaric bupivacaine. Twenty min after the spinal puncture, a controlled delivery topical cream containing either 25 mg ketamine (KG), 25 mg S(+)-ketamine (+KG) or placebo (PG) was applied. Pain and adverse effects were assessed postoperatively for 24 h. Intravenous ketoprofen was available at patient request. The plasmatic concentration of ketamine and S(+)-ketamine was measured prior the spinal puncture, 30 min, 4-hour, 8-hour, 16-hour and 24-hour after topical application by High Performance Liquid Chromatography (HPLC). Time to first rescue analgesic was longer to both KG and +KG (10 hours) compared to the PG (5 hours); ($p<0.05$). Ketoprofen consumption (mg) in 24 hour was higher in the PG compared to the others ($p<0.0005$). Thirty-min after the transdermal application, ketamine and S(+)-ketamine were detectable in plasma in both KG and +KG by HPLC, and showed a dose-ranging curve during the 24-hour evaluation ($p<0.02$). Adverse effects were similar among groups. As conclusions, transdermal 25 mg ketamine or 25 mg S(+)- ketamine similarly prolonged the duration of analgesia following orthopaedic procedures under bupivacaine spinal blockade, demonstrated by clinical and laboratorial data.

Keywords: Transdermal; Racemic ketamine; S(+)-ketamine; Postoperative analgesia

Introduction

Transdermal delivery of racemic ketamine was demonstrated to prolong epidural lidocaine analgesia after gynaecological surgery [1], to promote pain relief post-tonsillectomy [2], to meliorate pain symptoms after induced neuropathy [3,4] and to improve pain in different circumstances [5,6]. As an example, the topical application of a compounded amitriptyline-ketamine formulation improved pain in 75% of patients suffering from erythromelalgia [6] and the use of topical 10% ketamine, might be a useful tool for the treatment of Hidradenitis Supprurativa pain [7]. Proposed mechanisms of ketamine´s analgesia are controversial and include blockade of N-methyl-D-aspartate receptors in a non-competitive fashion [7], analgesia secondary to the absorption of topical ketamine into circulation [1,8-12], resulting in attenuation of central sensitization [10], or peripheral mechanism of action [13] at cutaneous nociceptors [14].

Because the potency of S(+)Ketamine was revealed to be two to threefold higher compared to the racemic compound [15-17], this study proposed to evaluate the analgesic effect of transdermal racemic ketamine compared to its S(+)-isomer in the perioperative setting. It was hypothesized that applying the same concentration of both drugs would result in double analgesic effect in the population receiving the S(+)-ketamine. Plasmatic measurements of ketamine/S(+)- ketamine was carried out to determine whether systemic absorption had occurred and corroborate to any analgesic effect from the transdermal system applied.

Methods

After ethic committee approval (Clinical trial HC) and written informed consent, 45 ASA status I and II patients scheduled for minor orthopaedic surgery (arthroscopy followed by meniscectomy), were computer-randomized to one of three groups and prospectively studied using a placebo-controlled double-blind design to examine analgesia and adverse effects (n=15). The surgeons responsible for the surgical procedures were the same in all cases. The concept of visual analog scale (VAS), which consisted of a 10 cm line with 0 equalling "no nausea" (VAS Nausea) or "no pain at all" and 10 equalling "worst possible nausea" or "the worst possible pain" was introduced before surgery.

Patients were premedicated with intravenous (IV) midazolam 0.05 mg/kg in the holding room. The final dose of IV midazolam was completed after the spinal injection in the operating room to 0.1 mg/kg. Hydration consisted of 10 ml/kg/h lactated Ringer´s solution after spinal anaesthesia. Spinal anaesthesia was performed in the operating room at the L3-L4 interspace with the patient in the sitting position. A total volume of 3 ml hyperbaric bupivacaine 0.5% (15 mg) was injected at 1 ml per 7 seconds through a 25-gauge intrathecal needle. Patients were placed supine immediately after spinal injection.

Twenty minutes after the spinal puncture (and before surgical stimuli) a transdermal cream system containing either 25 mg ketamine (K group (KG)), 25 mg S(+)-ketamine (+KG) or placebo (PG) was

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applied at the dominant upper arm, in a clean non-anesthetized area. The placebo and the ketamine/S(+)-ketamine transdermal systems were prepared by the Industrial Laboratory of the Faculty of Pharmaceutical Sciences of Ribeirão Preto- University of São Paulo and contained the same vehicle and similar physical and chemical properties, i.e., water/oil cream containing the penetration enhancer dimethyl sulfoxide (DMSO). The topical systems were developed and tested for controlled delivery of 25 mg of either drug. The rate of onset of ketamine/S(+)-ketamine release was 1.25 mg/h until the fourth hour, decaying to approximately 0.5 mg/h during the next 4 hours; then to approximately 0.4 mg/h during the subsequent 8 hours; to 0.3 mg/h during the subsequent 8 hours, and successively. Thus, 20% per cent of the active drug (5 mg) was available within 4 hours after the system application; 28% of the drug (7 mg) by 8-hour evaluation; 40.8% by 16-hour evaluation (10.2 mg); and finally 50.4% by 24-hour evaluation (12.6 mg).

One anaesthesiologist blind to the treatments applied the transdermal cream. Plasmatic measurements of ketamine/S(+)-ketamine was done through High Performance Liquid Chromatography (HPLC) [4,5]. Five-ml of venous blood was collected at the following times: 1) just prior the spinal puncture, 2) 30-min after transdermal cream application, 3) 4-hour, 4) 8-hour, 5) 16-hour and 6) 24-hour after transdermal cream application. The samples were collected in heparinized tubes and plasma was separated by centrifugation. The plasma samples were stores at –70°C until drug assay by HPLC system coupled to a positive ion electrospray mass spectrometric analysis. Solid-phase extraction was used for extracting analytes from dog plasma samples. The analytes were separated on a Zorbax SB C column with acetonitrile-formatted buffer as mobile phase. Detection was operated under selected ion monitoring mode. The analytes were stable during all sample storage, preparation and analysis procedures, in accordance to others [18].

The thoracic dermathomal sensorial level of anaesthesia was measured 5 and 10 min after the spinal punction. Blood pressure was monitored noninvasively every 5 min throughout surgery, and heart rate and oxyhaemoglobin saturation (SpO2) were continuously monitored throughout surgery. A decrease in mean arterial pressure greater than 15% below pre-aesthetic baseline was treated by incremental doses of ephedrine, 5 mg IV. Decreases in heart rate below 50 bpm were treated with incremental doses of atropine, 0.5 mg IV. The patient using the 10 cm VAS Nausea scored intraoperative nausea. The number of patients having nausea (of any degree) or vomiting at any point intraoperatively was noted. Nausea greater than 2/10 cm at any time or vomiting during the study were treated with metoclopramide 10 mg IV followed by ondansetron 4 mg IV, if necessary. Any other adverse effects were noted and treated, if necessary.

Postoperative assessment was done by a blinded investigator and included pain scores at the time of first rescue analgesic and at 24-hour after the spinal puncture, adverse effects and the duration of motor block, measured from aesthetic injection until the time to reach Bromage 2 score, defined as time since the spinal puncture until possibility to move the feet, but not bending the knees [19]. Duration of effective analgesia was measured as time from the spinal drug administration to the patient's first request for analgesic administration in the recovery room, recorded in min. The VAS at the time of first rescue analgesic medication was measured using the 10 cm VAS. Ketoprofen (50 mg IV) at 4-hour interval was available at patient request. If patient still complained of pain VAS>4 cm 30 min after the ketoprofen administration, 1 g IV dipyrone was available at a minimum 6-hour interval. The 24-hour VAS pain score reflected the patient's overall impression of the 24-hour following spinal injection. Postoperative adverse effects assessed included incidence of nightmares and hallucinations, and inability to concentrate or to answer to simple questions (about localization in time and space and what was the patient doing at the hospital). The 24-hour VAS pain score and VAS Nausea reflected the patient's overall impression of the 24-hour following epidural injection. Blood pressure and pulse rate were assessed postoperatively at 4-hour interval.

Statistics

The number of subjects was based upon preliminary experimental data to estimate the required sample size when comparing three treatment groups by analysis of variance. We hypothesized that transdermal 25-mg ketamine would increase the time to first rescue analgesic by 100% when compared to the placebo group, and that (S)+-25-mg Ketamine group would duplicate the racemic transdermal Ketamine. If we estimated a standard deviation for this prospective power analysis an 80% and an alpha value of 0.05, these assumptions would require 12 patients in each group to see a 100% increase in the time the first rescue analgesic. We elected to observe 15 patients in each group in order to overcome any patient´s exclusions due to uncollected data. The normality of the distributions was assessed using the Shapiro-Wilk's test. Groups were compared for demographic data (age, weight, height) and duration of surgery by one-way ANOVA. Incidence of adverse events, gender, ASA status and adjuvant drug use were compared among groups by Chi-square corrected for multiple comparisons. P was considered significant if <0.0166 (0.05 divided by the number of groups). Blood pressure, heart rate, level of anaesthesia (pinprick) and VAS scores were compared among groups by two-way ANOVA for repeated measures. Tukey analysis was applied to decrease the probability of type I error. The time to first rescue analgesics, the plasmatic values of ketamine/S(+)-ketamine, and the number of rescue analgesics in 24-h were compared using Kruskal-Wallis test, followed by the Wilcoxon rank sum test, while data within the same group were compared by Friedman test followed by the Wilcoxon rank sum test. P<0.05 was considered significant. Data are expressed as mean±SD, otherwise stated.

Results

All forty-five patients evaluated were submitted to both knee arthroscopy and meniscus repair, characterized as minor orthopaedic procedure. The decision for this surgical procedure was secondary to our interest in evaluating the somatic nociceptive type of pain, as other types of pain, such a as neuropathic pain, have already been evaluated [3-5]. The three groups showed no differences regarding ASA status, gender, age, weight, height, and surgical time (p>0.05, Table 1). The sensory loss assessment by pinprick test at 5 and 10 min measured in thoracic dermatomes (T) were similar among groups (Table 2, p>0.05). Related to ephedrine consumption, 3 patients in the PG and KG, and 2 patients in the +KG received 10 mg ephedrine, intraoperatively (p>0.05). The mean blood pressure and pulse rate at 0, 20, 40, 60, 80 and 100 min after the spinal injection were also the same in both groups (data not shown, p>0.05). None of the patients from any groups had intraoperative vomiting or had hallucination, complained of nausea or other adverse effects.

The postoperative data are represented in Table 2. The time measured from the spinal puncture to reach Bromage 2 was similar among groups (p>0.05). The VAS pain score at the time of first rescue analgesic medication was similar among groups. Three patients in

	ASA status (I/II)	Gender (M/F)	Age (years)*	Height (cm)*	Weight (kg)*	T 5-min+	T 10-min+	Surgical time (min)*
PG	11/4	5/10	41 ± 13	162 ± 9	66 ± 13	10 (7-10)	8 (6-8)	104 ± 45
KG	10/5	6/9	42 ± 15	163 ± 8	63 ± 9	10 (8-10)	8 (6-7)	104 ± 35
+KG	9/6	5/10	40 ± 13	161 ± 8	66 ± 14	10 (8-10)	8 (6-8)	111 ± 39

p>0.05 Data are expressed as mean ± SD and median (quartile ranges)
ASA- American Society of Anesthesiology; M/F- Male/Female; T- sensory thoracic dermathomal level (T1-T12) measured 5 and 10 min after the spinal puncture by pinprick.

Table 1: Demographic and intraoperative data

	PG	KG	+KG	p
Time to Bromage 2 (min)	183 ± 40	176 ± 47	170 ± 32	p>0.05
Time to first rescue analgesia (min)	298 ± 67	657 ± 422	628 ± 428	*
Ketoprofen consumption in 24 hours (mg)	233 ± 82	113 ± 74	103 ± 72	**
VAS at first rescue analgesic (cm)	6.6 ± 0.9	6 ± 0.8	6 ± 0.7	p>0.05
VAS 24-hour (cm)	2.5 ± 1	2.2 ± 2	2.3 ± 2	p>0.05

Data expressed as mean ± STD; VAS- visual analogue scale;
* KG was similar to +KG; KG>PG (p<0.02); +KG>PG (p<0.05);
**KG was similar to +KG; KG<PG (p<0.0005); +KG<PG (p<0.005).

Table 2: Postoperative pain data

both the KG and the +KG did not request any analgesic in 24-hour evaluation. The time to first rescue analgesic medication (min) was longer to both the KG and +KG compared to the PG (p<0.05). The number of rescue analgesic dose injections in 24-hour was higher in the PG compared to the others (p<0.005, Table 2). Patients only requested ketoprofen; therefore IV dypirone was not administered to any patient. The 24-hour VAS pain scores were similar to all groups (p>0.05). The plasmatic blood levels measured by HPLC of ketamine and S(+)-ketamine at the times: 1) 30-min, 2) 4-hour, 3) 8-hour, 4) 16-hour and 5) 24-hour after transdermal application are described in Table 3. The plasma concentration for PG was "zero" all times of evaluation, as were the plasma concentrations of all patients "just prior to the spinal" (data not shown). Thirty-min after the transdermal application, detectable levels of plasmatic ketamine and S(+)-ketamine were observed in the KG and +KG, respectively, while no detectable level of either drug was detected in the PG at any time, however not statistically significant (p>0.05). Four hours after the transdermal application, plasmatic levels of both ketamine and S(+)-ketamine were measured in the KG and +KG (p<0.005, compared to the PG). From time 30-min to 24-hour evaluation, both KG and +KG showed a similar dose-ranging curve (p<0.02). Plasmatic levels of both ketamine and S (+)-ketamine were similar to each other when individually evaluated at each distinct time (30-mim, 4-hour, 8-hour, 16-hour and 24-hour, p>0.05, Table 3), but always higher when compared to the PG (p<0.005).

Postoperatively, none of the patients complained of any adverse effects such as nightmares, had hallucinations, hypertension, tachycardia or showed any difficulty to concentrate, difficulty to answer to the simple questions formulated, or had other adverse effects.

Discussion

The results showed that in the population of the study, a controlled transdermal delivery of either 25 mg ketamine or 25 mg S(+)-ketamine similarly prolonged the time to first rescue analgesic medication (10 hours) compared to the PG (5 hours), similarly reduced the rescue analgesic consumption of ketoprofen in 24-hour evaluation, and similarly displayed a dose-range curve during the 24-hour evaluation, suggesting an analgesic action secondary to systemic absorption, once the site of surgery was the knee, and the site for the topical ketamine/S(+)-ketamine application was the arm.

The analgesic action of transdermal ketamine or S(+)-ketamine analgesia could be due to a central effect, a peripheral effect [20-22] or both, secondary to its plasmatic absorption [1,7-11]. Studies in volunteers described the isomer S(+)-ketamine as a potent analgesic at already low plasma concentrations [23], even at sub anaesthetic plasmatic doses [24]. It was suggested that benefits of ketamine may transcend its timely action, suggesting an anti-hyperalgesic action [25]. IV ketamine had a morphine-sparing effect after orthopaedic surgery, and also facilitated rehabilitation at one month and decreased postoperative chronic pain up to six months after surgery [26]. It was suggested that while S(+)ketamine's effect on acute experimental pain was driven by pharmacokinetics, its effect on chronic pain persisted beyond the infusion period when drug concentrations were below the analgesia threshold for acute pain, indicating a modulatory role for ketamine in chronic pain states [27]. Ketamine also enhances the descending inhibiting serotoninergic pathway, exerts antidepressive effects and analgesia persists for plasma concentrations ten times lower than hypnotic concentrations [28]. Among possible mechanisms of action, preferential inhibition of microglial channels in addition to neuronal N-methyl-*D*-aspartate (NMDA) receptors may account for the analgesic effect of S(+)-ketamine [29]. In addition, R(-)- and S(+)-Ketamine metabolites were described as analgesics through action at α7-nicotinic acetylcholine receptor, which may contribute to the final analgesic effect [30]. In addition, systemically administered ketamine has been described to have local aesthetic and anti-inflammatory actions such as inhibition of transcription factors activator protein 1 and nuclear factor-kappa-B, interleukin-8 production, as well as CD11b and CD16 expression, as well as spinal effects possibly involving desensitization of NMDA receptors in the spinal cord or restoration of inhibitory sensory control in the brain [15,27,31]. N-methyl-D-aspartate receptors also are located peripherally on sensory afferent nerve endings, and this provided the initial impetus for exploring peripheral applications of ketamine. After topical (e.g., as gels, creams) and peripheral application (e.g., localized injections), local tissue concentrations are higher than those after systemic administration and could engage lower affinity mechanisms [32].

Diversely from which we expected, the analgesia data between the S(+)-ketamine and the ketamine groups was similar, in contrast to previous description that the S(+)-isomer was approximately twice as potent as analgesic as the racemic ketamine in experimental (14) and in

	30-min after patch (µg/mL)	4-hour after patch (µg/mL)	8-hour after patch (µg/mL)	16-hour after patch (µg/mL)	24-hour after patch (µg/mL)	p
KG	0.00018 ± 0.00051	0.054 ± 0.018	0.082 ± 0.023	0.081 ± 0.026	0.078 ± 0.028	*
+KG	0.00024 ± 0.00072	0.053 ± 0.025	0.081 ± 0.019	0.08 ± 0.027	0.077 ± 0.026	**

Data expressed as mean ± STD.
-Comparison in the KG at the different tomes: (KG 24-hour = KG 16-hour = KG 8-hour)> KG 4-hour > KG 30-min > KG (p<0.02)
-Comparison in the +KG at the different times: (+KG 24-hour = +KG 16-hour =+KG 8-hour) > +KG 4-hour > KG 30-min (p<0. 02)
-Groups KG and +KG were similar to each other when both were compared at each time interval (P>0.05)

Table 3: Venous plasmatic ketamine and S(+)-ketamine levels measured by High Performance Liquid Chromatography at different times after transdermal patch ketamine or K(+)-ketamine application

animals [16,17]. Several factors could have influenced the results. In the present study we evaluated orthopaedic surgery, which is an example of acute somatic pain. Specifically, animal data indicate analgesic effects of low-dose ketamine on acute visceral pain and indicate a smaller effect on acute somatic pain [1]. Diversely from the topical systems we have tested for controlled delivery of 25 mg of either ketamine/S(+)-ketamine, topical ketamine has been used as compounded formulations alone in concentrations from 0.5% to 20% or in combination with other (co) analgesics. Its efficacy may depend on the choice of vehicle, the concentration and the pain state [33]. Other explanations why topical 25 mg ketamine was similar to 25 mg S(+)-ketamine, contrary to our expectations, are detailed. First of all, the analgesic exacerbated action of S(+)-ketamine seems to be species dependent [34-36]. The second point is the possibility of only the isomer S(+)-ketamine is indeed the analgesic in the racemic preparation. Following induced peritonitis in rats, topical administration of the racemic ketamine or its isomer S(+)ketamine equally reduced colonic inflammation, while the isomer R(-)ketamine was inactive [34]. The authors concluded that the final analgesic action of racemic ketamine was due to the isomer S(+)ketamine [34], what could explain the similar results obtained in the present study. Finally, the third explanation was that influence of gender. S(+)-ketamine displays clinically relevant sex differences in its pharmacokinetics, with a 20% greater elimination clearance of S(+)-ketamine and S(+)-norketamine in women resulting in higher drug plasma concentrations in men [23]. Nevertheless, in our study, all groups were demographically similar related to gender, with 6/9 and 5/10 male/female ratio for the KG and +KG, respectively (Table 1).

In the present study, with the controlled transdermal system used, the rate of onset of ketamine/S(+)-ketamine release was 1.25 mg/h until the fourth hour, decaying to approximately 0.5 mg/h during the next 4 hours; then to approximately 0.4 mg/h during the subsequent 8 hours; to 0.3 mg/h during the subsequent 8 hours, and successively, what could explain why the plasmatic dosage concentration was similar from 8-hour to 24-hour evaluation for both KG and +KG. As a result, the release pattern of the system allowed us to calculate the available drug to be: 5 mg at 4-hour, 7 mg at 8-hour, 10.2 mg at 16-hour and 12.6 mg at 24-hour evaluation. It means that only half of the drug (12.6 mg) was in fact available in 24-hour. Recently, different transdermal ketamine preparations (hydrogel, cream or organogel) were evaluated and demonstrated no significant difference among them related to plasmatic ketamine levels [8].

In conclusion, transdermal delivery of either 25 mg ketamine or 25 mg S(+)-ketamine similarly prolonged the duration of analgesia following orthopaedic procedures under bupivacaine spinal blockade, demonstrated by clinical and laboratorial data, indicating that the final analgesic action was a result of the systemic absorption of the drug. New research directions should provide insights and novel therapeutic strategies for clinical use of transdermal ketamine/S(+) in other types of pain, and future trials of topical ketamine/S(+)-ketamine should include a consideration of factors that could predispose to favorable outcomes.

Author's contributions

Gabriela R Lauretti: study design, selecting patients, statistics, discussion and writing the data.

Marcia Amaral: getting the signature in the written informed consent, anaesthesia, collecting blood samples and taking appropriate care of their store, postoperative data collection.

Ramon Dangelo Dias: anaesthesia, data collection, discussion of the data.

Vera Lucia Lanchote: All plasmatic measurements.

Anita L Mattos: anesthesia, postoperative data collection, discussion of the data.

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