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Analgesic Efficacy of the Intra-articular Administration of S(+)- Ketamine in Patients Undergoing Total Knee Arthroplasty

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Summary: Guará Sobrinho H, Garcia JBS, Vasconcelos JW, Sousa JCA, Ferro LSG. Analgesic Efficacy of the Intra-articular Administration of S(+)- Ketamine in Patients Undergoing Total Knee Arthroplasty.

Background and objectives: Total knee arthroplasty (TKA) is associated with significant postoperative pain. Many intra-articular (IA) agents have been used for postoperative analgesia with inconsistent outcomes. Ketamine's enantiomer S(+), S(+)- ketamine, was recently introduced commercially, with higher analgesic potency and less side effects than the racemic form. An experimental prospective randomized double-blind study was conducted to evaluate the analgesic efficacy of intra-articular S(+)- ketamine in patients undergoing primary TKA.

Method: In total, 56 patients were evaluated and allocated into three groups: Group A (n = 19) received 0.25 mg.kg^{-1} of S(+)- ketamine diluted in 20 mL of saline solution 0.9%; Group B (n = 17) received 0.5 mg.kg^{-1} of S(+)- ketamine diluted in the same way; and Group C (n = 20) received only 20 mL of intra-articular saline 0.9%, immediately after surgery and drain placement. All patients had access to rescue analgesic therapy, with the use of intravenous morphine alone. Evaluations were made 2, 6, 12, and 24 hours postoperatively, with measurement of pain intensity by Visual Analogue Scale (VAS), use of rescue medication by the evaluation of the time elapsed between the intra-articular injection of the solution and first dose of rescue, total consumption within 24 hours, and adverse effects.

Results: The S(+)- ketamine groups had lower pain scores compared with the saline group. The lowest dose of intra-articular S(+)- ketamine (Group A: 0.25 mg.kg^{-1}) resulted in better pain scores and less rescue analgesia, with longer time to first request. Adverse effects were infrequent. The results with lower pain scores in groups using S(+)- ketamine are a trend, as there was no statistical significance between groups.

Conclusion: In this study, with this sample, the analgesic effect of IA S(+)- ketamine was not superior to saline solution in the postoperative period of TKA.

Keywords: Analgesia; Injections, Intra-articular; Ketamine; Isomerism; Arthroplasty, Replacement, Knee.

INTRODUCTION

Severe pain is the main indication for total knee arthroplasty (TKA), which is successful in patients with advanced primary or secondary osteoarthritis when all non-surgical options have been used without success [1,2]. Even positive radiologic images depend on a clinical correlation manifested by pain to be a surgical indication [1,2].

Several authors describe the postoperative period of such procedure as intensely painful and associated with high demand for analgesics [3,4,5]. The use of systemic medications, central or peripheral blocks, and intra-articular analgesics for postoperative pain management have limitations related to special equipment and monitoring, in addition to significant adverse effects [6]. Thus, promoting analgesia only at the site of surgical trauma with minimal systemic effects is an attractive option [7].

Many intra-articular (IA) agents, such as morphine and bupivacaine, have been used for local anesthesia and postoperative analgesia in treatment and prevention of pain after knee surgeries. Ketamine has been of little use via IA. However, studies suggest that this drug may be useful as an adjuvant analgesic administered by this route [8-11].

Ketamine has been introduced into clinical practice for nearly 40 years, with the objective to act as a mono-anesthetic substance with analgesia, amnesia, unconsciousness, and immobility properties. Due to its significant adverse effects, ketamine has not gained wide clinical acceptance. Dextro salt

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of ketamine, isomer S(+) ketamine, was recently released, which has similar properties to the racemic form, greater analgesic potency, and fewer side effects, arousing a renewed interest in this drug [12].

S(+)- ketamine proved to be four times more potent than R(-) ketamine and produced adequate anesthesia in 95% of cases. The emergency reactions, such as delusions or hallucinations, decreased from 37% with R(-) ketamine to 5% with S(+)- ketamine. It is a good choice for postoperative analgesia, with adequate power, safety of non-respiratory depression, neuroprotection (cerebral vasodilation), and cardiac protection [13].

Borner et al. [11] used IA S(+)- ketamine in postoperative (PO) knee arthroscopy and concluded that there was a reduction on the level of subjective pain and opioid consumption compared with the application of IA bupivacaine and saline.

In a meta-analysis of 53 articles on ketamine, the authors found only four studies of S(+)- ketamine, none with administration by the intra-articular route [14]. The lack of published articles assessing the use of intra-articular S(+)- ketamine in PO of TKA leads us to consider this route as an option requiring a systematic and well-controlled study.

The aim of this study was to evaluate the analgesic efficacy of intra-articular S(+)- ketamine in patients undergoing primary total knee arthroplasty.

METHOD

Experimental prospective randomized double-blind study conducted at the Department of Orthopedics of the HU-UFMA, from March 2009 to December 2010. Were included 60 patients referred for total knee arthroplasty, unilateral, with a diagnosis of primary osteoarthritis. It was found that samples with a minimum of 17 patients per group are needed in order to obtain an 80% chance of detecting a difference of 1 cm on a visual analgesic scale with a 5% confidence level [6].

Exclusion criteria were patients who refused to participate, classified as ASA IV or V by the American Society of Anesthesiologists, with psychiatric illness, drug addicts, with cardiovascular, respiratory, metabolic or neurological diseases, decompensated, and with recognized allergy to anesthetics. Were also excluded patients who used postoperative analgesics other than the one recommended as rescue and those who were discharged before the first 24 hours postoperatively.

All procedures were performed under spinal anesthesia, which was administered by a staff anesthesiologist of the Hospital Universitário Presidente Dutra, with application of 15 mg of isobaric bupivacaine 0.5% without associated opioids. The use of benzodiazepines for patient sedation was allowed at the discretion of the anesthesiologist.

Limb preparation consisted of placing a pneumatic cuff at the root of the thigh, and the joint approach was performed through midline incision, with luxation and lateral rotation of the patella. Prosthesis model Insall III (Meta-Bio® and Baumer®) was used, cemented, without inclusion of patellar prosthesis.

After the procedure, local hemostasis was performed, with placement of suction drain through a different opening wound, followed by synthesis of the plans of the wound. Before complete closure of the skin, patients underwent intra-articular injection of the solution determined for each case. In all patients, we waited 15 minutes before opening the drain.

Patients were assigned in groups A, B or C through a random selection of sealed envelopes, without the participation of the investigator, patient, or surgeon. The solution was prepared according to the group distribution and taken to the operating room identified only by the case number. Group A (n = 19) received 0.25 $mg.kg^{-1}$ of S(+)- ketamine diluted in 20 mL of saline solution 0.9%; Group B (n = 17) received 0.5 $mg.kg^{-1}$ of S(+)- ketamine diluted in the same way; and Group C (n = 20) received only 20 mL of intra-articular saline 0.9%, immediately after the procedure and drain placement.

All patients had access to rescue analgesia. Morphine alone was used at a dose of 5 mg IV, at the request of the patient, with a minimum of four hours between doses. In case of moderate to severe pain in less than four hours or persistence of pain, an additional dose of 5 mg could be used, with annotation in protocol form, which consisted of patient's identification and pain control and adverse events evaluation.

Patient's identification data were collected on age, sex, weight, height and time of operation.

Regarding pain control evaluation, systematic assessments were made at times t_1 - 2 hours PO; t_2 - 6 hours PO; t_3 – 12 hours PO, and t_4 - 24 hours PO. Measurement of local pain intensity at rest was performed using Visual Analogue Scale (VAS), previously instructed to patients. This scale consists of a 10 cm line in which one end (0 cm) indicates no pain and the other end (10 cm) indicates the worst possible pain [15].

The use of rescue medication was also assessed by the time (Tr) elapsed between the intra-articular injection of the solution and the first rescue dose and its total consumption within 24 hours, quantifying the number of doses taken.

Patients were asked about the emergence of adverse effects through a questionnaire assessing dizziness, nausea, vomiting, itching and/or hives, restlessness, disorientation, depression, drowsiness, delirium, hallucinations, amnesia, and some other effects, voluntarily reported.

Results were tabulated in an electronic database program and exported to Stata 9.0™ for statistical analysis. To detect whether variables were normally distributed Shapiro-Wilk test was used followed by parametric tests for variables following a normal distribution and nonparametric for the others.

Anthropometric data were compared by ANOVA. Kruskal-Wallis test was used for weight and age variables and chi-square test for gender and adverse effects. A significance level of 5% in all tests was adopted. The study protocol was approved (Nº 293/2008) by the Research Ethics Committee of the Hospital Universitário da Universidade Federal do Maranhão (HU-UFMA), and all patients signed the informed consent before the first evaluation.

RESULTS

Among the 60 patients, one was lost in Group A and three in Group B due to the intravenous administration of non-recommended analgesic and morphine during spinal anesthesia. Therefore, we assessed a sample of 56 patients, Group A (n = 19), Group B (n = 17), and Group C (n = 20). The mean duration of surgery was 128 minutes, with no statistically significant difference between groups for the studied variables sex, age, weight, and height (Table I).

Table II shows the mean value of pain intensity at different times "t" for each group analyzed. There was no statistically significant difference among S(+)- ketamine groups (A and B) and saline group (C).

Regarding the comparison of rescue medication, Group A had a lower consumption than Groups B and C, but with no statistical significance (p = 0.52). The average consumption over 24 hours was 2.47 morphine doses for Group A, 2.82 for Group B, and 2.9 for Group C. Graphic 1 shows the total consumption for each group throughout the study.

The time to the first dose of rescue analgesic was longer in Group A than in Groups B and C. There was a mean of 177.4 minutes for Group A, 157.9 for Group B, and 145.1 for Group C, with no statistical significance (p = 0.35). Graphic 2 represents the medians, the minimum and maximum values for the time in minutes in which patients requested morphine rescue.

Table I – Anthropometric Data of Evaluated Patients

Variables		Group A (n = 19)	Group B (n = 17)	Group C (n = 20)	p
Gender (%)*	M	15.79	5.88	30	0.43
	F	84.21	94.12	70	0.65
Age (years)**		67.05 ± 7.04	64.12 ± 8.90	66.65 ± 8.27	0.72
Weight (kg)**		66.85 ± 12.99	65.26 ± 10.47	67.87 ± 13.91	0.88
Height (cm)**		151.42 ± 9.96	151.71 ± 6.11	150.95 ± 8.80	0.96

*Percentage. **Mean ± standard-deviation. Statistical significance when p < 0.05. ANOVA Test. Kruskal-Wallis Test. Chi-square Test. M: male; F: female.

Table II – Mean Values ± Standard Deviation of Pain Intensity for Each Interval Measured by VAS

Variables	Group A (n = 19)	Group B (n = 17)	Group C (n = 20)	p
t1	(4.6 ± 3.8)	(6.4 ± 3.0)	(6.7 ± 3.0)	0.23
t2	(4.8 ± 2.9)	(5.8 ± 3.1)	(5.5 ± 3.1)	0.68
t3	(5.1 ± 2.8)	(5.2 ± 3.0)	(5.0 ± 2.8)	0.79
t4	(3.1 ± 2.4)	(3.1 ± 2.3)	(3.2 ± 2.8)	0.76

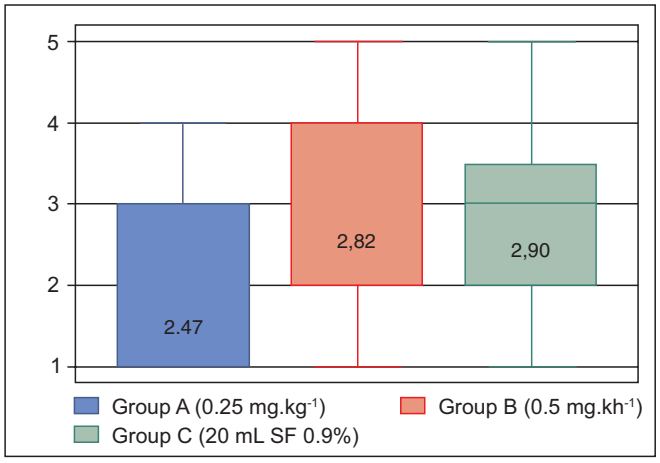
Values are expressed as mean ± standard deviation. Statistical significance at p < 0.05. Kruskal-Wallis test.

Some adverse effects were observed, with nausea, dizziness, and somnolence being the most prevalent, but with no statistical difference between groups, as shown in Table III.

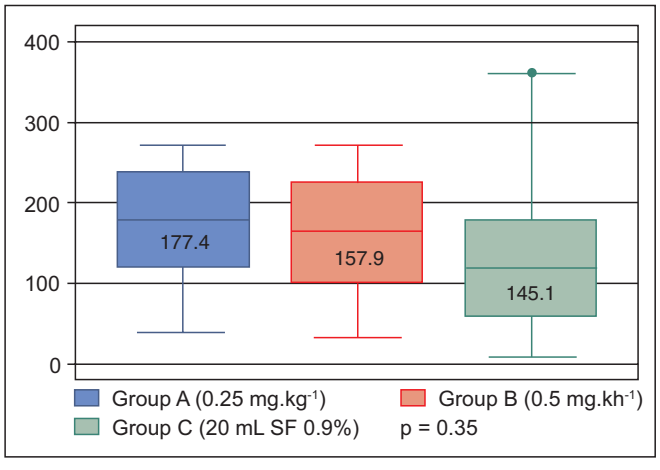
Table III – Number of Patients (n) and Percentage (%) of Adverse Effects Found in Studied Groups

Collateral effects	Group A		Group B		Group C		p
	n	%	n	%	n	%	
Nausea	8	42.11	6	35.29	7	35.00	0.54
Dizziness	3	15.79	5	29.41	1	5.00	0.34
Drowsiness	1	5.26	4	23.53	4	20.00	0.57
Hallucination	1	5.26	0	0	1	5.00	0.65
Nightmares	1	5.26	0	0	0	0	0.32
Delirium	2	10.53	0	0	0	0	0.49

Chi-square test. Statistical significance at p < 0.05.



Graphic 1 – Median and Quartiles of the Number of Doses of Morphine in the period of 24 h.



Graphic 2 – Median and Quartiles Regarding Time (minutes) of Rescue analgesic in Studied Groups.

DISCUSSION

Many studies of IA medication use are for arthroscopic knee surgery, a procedure less painful than TKA, which used bupivacaine [16], morphine [17], clonidine [18], and magnesium [19] with satisfactory results. Ketamine is rarely used, but it has been reported as an analgesic able to produce effect in peripheral pain control [9,20-22].

The choice of S(+)- ketamine was based on analysis of studies demonstrating that this drug is an anesthetic and analgesic agent with fast onset of action, with non-competitive blocking action on the N-methyl-D-aspartate (NMDA) receptor, placing it at an unique level in combating the painful process [9,23,24]. Due to the adverse effects following systemic administration, local application of NMDA antagonists has become a promising option. Subsequent studies have used intra-articular, topical or local injections of ketamine to minimize these effects, reduce pain and consumption of opioids in the postoperative period [24-26].

Similar to other studies, there was no difference between groups for age, sex, weight, height, and duration of surgery, which provides a sample with uniform demographic data [6,9,11,17,24,25,27-34].

The assessment of S(+)- ketamine analgesic efficacy was divided into direct and indirect; the first was based on comparative analysis of pain scores obtained from VAS at time (t) between groups; in the second, we evaluated the comparison between groups with respect to time (Tr) for the first request of rescue analgesia and its total consumption.

Rosseland et al. [25], Borner et al. [11], and Garcia et al. [35] have used this type of analysis in their work, which follows the general trend of most studies on this topic. We believe this is the best way to evaluate the efficacy of therapy, because, whereas the effect of intervention with rescue analgesics tends to homogenize VAS scores, the analysis of indirect data allows characterizing the effectiveness of IA S(+)- ketamine with more reliability.

Patients were evaluated postoperatively at t1 (2h), T2 (6h), T3 (12h), and T4 (24h) based on earlier publications and assessment division of post-operative pain in three phases: early (0-2h) in which the residual effect of anesthesia/analgesia administered intraoperatively could lead to a bias in the study; intermediate (2-6h) in which the effect of these drugs usually start to decrease, and late (6-24h) in which the present analgesic effect would be predominantly local [36-38].

In order to reduce the influence of the anesthetic procedure in the evaluation of t1, we chose to administer spinal anesthesia without the addition of opioids and with no use of local anesthesia. There was no association of analgesic drugs at any time of the procedure or postoperatively.

In direct evaluation, we found lower pain scores on VAS in Group A at t1 and t2 compared with other groups, but with no statistical significance. In Groups B and C, the assessment of pain scores from t1 to t4 showed a decreasing trend in the intensity of pain over time. There was no statistically significant difference between groups, although S(+)- ketamine groups (A and B) had lower pain scores.

Intra-articular morphine at high doses (10 mg) was tested on postoperative TKA, with lower pain scores, consumption, and time of rescue analgesia compared to placebo [35]. Fu et al. [7], used morphine 5 mg, bupivacaine 15 mg, and betamethasone 1 mL intra-articularly in postoperative TKA and found lower pain scores. Carvalho Junior et al. [39] showed that intra-articular and peri-incisional administration of bupivacaine, morphine, and epinephrine were ineffective in reducing postoperative pain in TKA. Ritter et al. [33] also used intra-articular morphine and bupivacaine on postoperative TKA and found no improvement in analgesia.

Dal et al. [9] used IA racemic ketamine at a dose of 0.5 $mg.kg^{-1}$ and promoted prolonged and effective analgesia with few adverse effects, with similar results to those of neostigmine but no better than bupivacaine. Rosseland et al. [25] studied 77 patients after the use of racemic ketamine 10 mg IA and 10 mg intramuscular compared with saline solution 10 mL IA in knee arthroscopy and there was no difference between the group receiving racemic ketamine and saline, both through IA route.

We found no studies of IA S(+)- ketamine in postoperative TKA. There is a study by Borner et al. [11] in which IA S(+)- ketamine was used, but in postoperative knee arthroscopy, and the authors concluded that the dose 0.25 $mg.kg^{-1}$ decreased pain intensity and opioid consumption if compared with the administration of IA bupivacaine and saline. In our study, the dose of 0.25 $mg.kg^{-1}$ showed a trend in reducing pain scores and opioid consumption, similar to Borner et al. [11], but there was no difference, both in statistics or in the procedure that generates more nociceptive stimuli.

Another way to test S(+)- ketamine would be through continuous intra-articular injection by a catheter in the postoperative period, at various doses, and not only one application immediately after the procedure. Bupivacaine was tested intra-articularly before and after knee arthroscopy, with better results in controlling pain when administered before surgery, suggesting a preemptive effect [40]. Because ketamine has been reported as effective in controlling postoperative hyperalgesia, it could also be used before the procedure to evaluate a possible preemptive action, as well as pain could be evaluated weeks after surgery to test its effect on chronic pain after surgery.

The rescue analgesic could be administered by infusion pump and controlled by the patient to prevent administration or request delay. This may be a relevant observation when high pain scores are found at times t1 to t3 (≥ 4) associated with low demand for rescue analgesic (< 3). One aspect to be emphasized is the culture that pain should be part of the postoperative period and that, despite the explanations given to the patient, many remain passive or stoic regarding analgesic request.

The ideal time of injected solution permanence into the knee before opening the drain tube should be better determined. Most studies using drain opens it between 10 min [17] and 15 min [35], due to a hyperkinetic blood flow there is a displacement of the drug from its peripheral receptor, which influences the quality and duration of analgesic effect. One

interesting possibility would be the non-use of suction drain, which would guarantee the permanence of the whole solution injected into the joint. A recent study showed no benefit in the use of suction drain in postoperative TKA [41].

The mean consumption of rescue medication within the first postoperative 24 hours was the first variable assessed in the indirect evaluation, which showed a tendency toward lower value in Group A than Groups B and C. Similar results were found by Borner et al. [11] and Dal et al. [9] The second variable studied was "Tr" (time to first request of analgesic dose) in which the group with the lowest dose of S(+)- ketamine had more prolonged analgesia, weighting longer to request rescue analgesia (177.4 min), with no statistical difference though. This result differs from that of Dal et al. [9] who found a greater time to first analgesic dose in groups receiving racemic ketamine 0.5 mg.kg^{-1}, with mean of 109.3 versus 63.3 min for the group receiving 20 mL of saline in postoperative knee arthroscopy.

There was occurrence of some adverse effects during the study, but none compromised its continuation. In previous work, the onset of side effects also was not a limiting factor for IA ketamine use [9,25]. The few side effects can be explained by the relatively low dose used, intra-articular poor vascularization, degree of synovectomy during surgery, or effect only locally. Studies are needed to determine the optimal dose of intra-articular S(+)- ketamine and evaluate its plasma concentration and its metabolites, in order to differentiate systemic from peripheral effect. An example is the study by Joshi et al. [17] that assayed plasma morphine and found very low concentration, insufficient to promote postoperative analgesia, which suggests only local effect.

To explain the lack of significance in pain scores between groups, we may consider some justifications, such as the small number of patients per group, residual effect of anesthetic due to the technique used, and possible preemptive effect of subarachnoid block, which could prevent the sensitization of spinal neurons and provide postoperative analgesia. Furthermore, the optimal dose and volume of S(+)- ketamine for intra-articular use should be better determined. It is known that the commonly used doses (5 mg.kg^{-1}-intramuscularly or 1-2 mg.kg^{-1} intravenously) are not ideal, as dysleptic phenomena often occur in patients. The benefits of S(+)- ketamine exist when it is used in small doses (0.1 to 0.25 mg.kg-^{1}) via parenteral route, due to its greater affinity for the NMDA receptors, which provides adequate analgesia and consumption reduction of analgesics postoperatively [12,41]. In our study, the lowest dose of S(+)- ketamine (Group A: 0.25 mg.kg^{-1}) showed the best trend toward reducing pain scores and also demonstrated the possibility of ketamine better effects at lower doses via intra-articular route.

In this study, the groups using S(+)- ketamine showed a tendency toward lower scores for pain in postoperative total knee arthroplasty, without significant superiority compared to saline.

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