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Comparison of Effectiveness of Four Subanesthetic Doses of Dextroketamine in Allaying Procedural Discomfort during Spinal Anesthesia: A Randomized Double Blind Trial

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Abstract

Background: Subarachnoid needle puncture generates discomfort during anesthesia spinal. Infiltration with local anesthetic and sedation is performed to provide analgesia and amnesia. The primary objective of the study was to compare the effectiveness of four different subanesthetic doses of dextroketamine for pain relief from the spinal anesthesia needle cut tip.

Methods: Patients with American Society of Anesthesiologists (ASA) Status I and II posted for elective surgeries under a subarachnoid block were randomized into 4 groups of 20 patients each. Group A received at dextroketamine 0.1 mg/kg, group B received at dextroketamine 0.15 mg/kg, group C received at dextroketamine 0.2 mg/kg and group D received at dextroketamine 0.25 mg/kg. Wilson score sedation, ease of positioning, prick response, nystagmus, hallucinations, change in heart rate, systolic blood pressure, decrease in oxygen saturation (<96%), apnea, airway obstruction, as well as other side effects and patient satisfaction were evaluated.

Results: There is a positive correlation between increasing ketamine dose and the degree of sedation and ease of positioning on the operating table for performing spinal puncture. There is a correlation showing negative association between increased dextroketamine dose and the response to the pin prick. There is a correlation between an increase in ketamine dose and the appearance of hallucinations. Nausea occurred in two patients with the highest dose.

Conclusion: Dextroketamine at a dose of $0.1 mg.kg^{-1}$ provides sufficient sedation to place the patient in position for spinal puncture and puncture pain relief in 50% of patients, without hemodynamic changes. The relief of pain and side effects are dose dependent.

Keywords: Subanesthetic dose; Ketamine; Subarachnoid block

Introduction

Spinal anesthesia for lower limb surgery offers significant benefits. These benefits include superior intraoperative pain control, attenuation of the surgical stress response, minimal systemic impairment, lower incidence of postoperative nausea and vomiting, excellent localized postoperative analgesia, and decreased hospital discharge time and cost [1]. Procedural discomfort is experienced during the establishment of spinal anesthesia even after good preoperative counseling and premedication. This could be due to multiple reasons such as cold operating environment, new people, positioning, the procedure itself and the possibility of multiple punctures. (Run-on sentence) To mitigate these problems and to increase patient comfort, sedation is performed to provide analgesia and amnesia [2]. Furthermore, patients would experience pain during the needle insertion in spite of administration of local anesthetic. Infiltration with local anesthetic is used to decrease the incidence of pain during spinal puncture with needles.

Ketamine was introduced as the sole anesthetic agent capable of promoting analgesia, amnesia, unconsciousness and immobility. The isomer S (+) ketamine could promote fewer side effects, reduced incidence of nausea compared to the racemic mixture [3]. Ketamine doses produce a dissociative anesthesia with sedation, analgesia and amnesia [4].

The primary objective of the study was to compare the effectiveness of the use of four subanesthetic doses of dextroketamine for pain relief from the spinal anesthesia needle cut tip. The secondary objectives were to evaluate the side effects of the four subanesthetic doses of dextroketamine in relation to the appearance of nystagmus, mild hallucinations, changes in heart rate and systolic blood pressure, oxygen saturation and satisfaction with the technique in the Post-Anesthetic Care Unit (PACU).

Methods

After registration in the Brazil Platform (CAAE: 34743214.9.0000.5179), approval by the ethics committee on research and signing of the informed consent, a double-blind randomized prospective study was performed in patients ASA physical status I and II (American Society of Anesthesiology), aged between 18 and 60 years old, weighing between 50 and 90 kg of both sexes indicated for orthopedic surgery of the lower limbs. Patients with heart or respiratory disease, mental disorder,

neurological disease, sensitivity to anesthetic or anticoagulant therapy were excluded.

Using a significance level of 5% and a margin of error of 0.10, sample size obtained was 62 patients. 18 patients were added with a total sample of 80 patients in four groups of 20 patients. Patients were randomized to one of four groups the sealed envelope technique. Group A received dextroketamine (Cristália Chemicals and Pharmaceuticals Ltd.) 0.1 $mg.kg^{-1}$, group B received 0.15 $mg.kg^{-1}$ dextroketamine, group C received 0.2 $mg.kg^{-1}$ dextroketamine and group D received 0.25 $mg.kg^{-1}$ dextroketamine intravenously. After opening the envelope, the drug was administered according to the dose in insulin syringe by an assistant.

No premedication was administered in the room. After venous puncture with 18G catheter was started, infusion of Ringer's lactate solution began. Monitoring in the operating room consisted of continuous ECG using the CM5 lead, blood pressure by non-invasive method and pulse oximetry.

After administration of midazolam (1 mg), level of sedation was assessed [5] (Table 1). After this evaluation, patient was administered intravenously dextrocetamine dose as their group. Between two to three minutes after administration of the dextrocetamine dose, its action was evaluated by the same sedation scale (Table 1). Ease of positioning for subarachnoid block (while turning the patient to the sitting position) was assessed by a two point scale: 1) patient sat down at the operating table without help and 2) with (confused as to what this means) help. With aseptic precautions, subarachnoid block was performed using a 27G (B.Braun Melsungen) cut spinal needle without local infiltration. The desired volume of 0.5% isobaric bupivacaine was injected intrathecally and was confirmed by the appearance of Cerebrospinal Fluid (CSF). Response to spinal needle insertion was noted and graded by a 4 point score (Table 2). Side effects such as nystagmus, hallucinations, change in heart rate, systolic blood pressure, decrease in oxygen saturation (<96%), apnea, airway obstruction were recorded. Time was observed between the ketamine injection and the end of anesthetic injection in the subarachnoid space. Then, the patient was placed in supine position for surgery, and a nasal catheter was placed with oxygen at 3 L/min. (I think it's neater). In the PACU, the patient was asked about the satisfaction with the question: if he or she would do that procedure again if medically necessary.

Demographic profile was expressed as mean ± SD. Hemodynamic parameters, Spo2, respiratory rate and verbal response were assessed by nonparametric Kruskal-Wallis test. Sedation score, ease of positioning and prick response were compared using a nonparametric Kruskal-Wallis test, which is the non parametric equivalent of one-factor ANOVA. Hallucinations, recall of procedure and patient satisfaction were assessed by chi-square test with Monte Carlo simulation. (Why would you use a Monte Carlo simulation? You have to justify it such as not enough data and if it is appropriate to use a Monte Carlo simulation to substitute for lack of data.) A value of $P<0.05$ was considered statistically significant.

Table 1: Wilson Sedation Scale (4).

Score	Clinic
1	Patient oriented, responds to simple questions
2	Sleepy patient, awake on command
3	Patient awakens only with mild physical stimulation
4	Patient awakens with no physical stimulus

Table 2: Response to spinal needle insertion.

Score	Response
0	Without any movement of the patient
1	Back muscle contraction
2	Minimal patient movement
3	Gross patient movement
4	Need more sedation

Results

There is no significant difference between the groups with regard to demographic characteristics and the time to blockade (Table 3).

The 1 mg dose of midazolam gave statistically the same effect in all patients, with no significant difference (Table 4).

Maximum sedation (a score of 4) after ketamine was not observed in any of the patients of four groups. A score of 3 was not observed in any patients in group A, 2 of them in group B, 6 of them in group C and 8 of them in the group D (Table 5). There was statistically significant difference in the degree of sedation when an intergroup comparison was made. Using the Spearman correlation revealed a positive correlation between increasing ketamine dose and the degree of sedation (r=0.537).

With regard to the ease of positioning, 17 patients in group A, 13 patients in group B, and 7 patients in group C turned on their own while only 2 patients in group D (Table 6). Ease of positioning was significantly different between the four groups. Using the Spearman correlation revealed a positive correlation between increasing ketamine dose and ease of positioning on the operating table for performing spinal puncture (r = 0.570).

When the response to prick was assessed, 18 patients in group D, 11 patients in group C and 10 patients in both group B and A, did not show any gross patient movement (Table 7). Prick response scores were significantly high in group A, B and C when compared to group D. The Spearman correlation showed negative association between increased ketamine dose and the response to the pin prick (r=-0260)

No statistically significant difference was found in oxygen saturation after midazolam and ketamine among the four groups. There was no oxygen saturation lower than 96% in any patient. With higher doses (C and D group) presented increased HR and SBP in three patients, with no significant difference (Table 8).

The chi-square test with a Monte Carlo simulation revealed that there is a correlation between the increase in ketamine dose

Table 3: Demographics data and the time to blockade (m ± SD).

Variables	Group A 0.1 mg/Kg	Group B 0.15 mg/Kg	Group C 0.2 mg/Kg	Group D 0.25 mg/Kg	*p-value*
Age (ys)	35.56 ± 15.04	35.72 ± 12.92	35.72 ± 12.92	35.72 ± 12.92	*0.936**
Weight (kg)	68.89 ± 9.25	68.89 ± 9.25	68.33 ± 9.25	65.17 ± 8.43	*0.086**
Height (cm)	168.0 ± 7. 35	167.5 ± 9.42	167.5 ± 9.42	167.5 ± 9.42	*0.687**
Gender: M / F	19 / 1	19 / 1	17 / 3	15 / 5	*0.203***
Physical Status: ASA	I =14 / II = 6	I =14 / II = 6	I = 14 / II = 6	I = 14 / II = 6	*0.700***
Time to blockade	6:09 ± 0:59	6:01 ± 1:13	6:09 ± 1:07	6:37 ± 1:24	*0.190**

* Kruskal-Wallis ** Chi-square test with Monte Carlo simulation

Table 4: Score of sedation after midazolam according to the group.

Sedation Score	Group A 0.1 mg/Kg	Group B 0.15 mg/Kg	Group C 0.2 mg/Kg	Group D 0.25 mg/Kg	*p-value*
1	19	20	20	19	*0.567*
2	1	0	0	0	
3	0	0	0	1	
4	0	0	0	0	

Table 5: Score of sedation after ketamine according to the group.

Sedation Score	Group A 0.1 mg/Kg	Group B 0.15 mg/Kg	Group C 0.2 mg/Kg	Group D 0.25 mg/Kg	*p-value*
1	17	13	6	4	*0.000*
2	3	5	8	8	
3	0	2	8	8	
4	0	0	0	0	

Table 6: Ease of positioning for subarachnoid block after ketamine according to the group.

Positioning Score	Group A 0.1 mg/Kg	Group B 0.15 mg/Kg	Group C 0.2 mg/Kg	Group D 0.25 mg/Kg	*p-value*
1	17	13	13	2	*0.000*
2	3	7	8	18	

Table 7: Score of response to spinal needle insertion.

Response Score Spinal Needle	Group A 0.1 mg/Kg	Group B 0.15 mg/Kg	Group C 0.2 mg/Kg	Group D 0.25 mg/Kg	*p-value*
0	10	10	11	18	*0.046*
1	6	6	5	1	
2	4	2	3	1	
3	0	0	1	0	
4	0	1	0	0	

Table 8: Hemodynamic and respiratory effects of ketamine.

Effects	Group A 0.1 mg/Kg	Group B 0.15 mg/Kg	Group C 0.2 mg/Kg	Group D 0.25 mg/Kg
Increase HR	0	0	2	1
Increase SBP	0	0	1	1
Decrease SpO_2	0	0	0	0

HR: heart rate; SBP: systolic blood pressure; SpO_2: oxygen saturation

and the appearance of hallucinations (C = 0.445, Contingency coefficient). Using the same test, there was no correlation between increasing dose and the appearance of nystagmus (Table 9).

Among the 80 patients studied only two (C and D group) were not satisfied with the method, justified by the appearance of hallucinations. Nausea occurred in two patients with the highest dose.

Table 9: Colateral effects of ketamine.

Colateral Effects	Group A 0.1 mg/Kg	Group B 0.15 mg/Kg	Group C 0.2 mg/Kg	Group D 0.25 mg/Kg	*p-value*
Nystagmus	6	9	11	11	*0.34*
Hallucinations	1	2	5	12	*0.00*

Discussion

In the present study, patients who received subanesthetic dose ketamine tends to have lower incidence of pain during spinal puncture with cutting needle. This study also showed that sedation, ease of positioning the patient, decreased pain to the pin prick and the appearance of hallucinations was dose-dependent. Different doses produced different results, but the time for blockade was the same in all groups.

Clinically, ketamine is administered as a racemate composed of two optical isomers, S(+) and R(-). Early observations suggested that analgesia following ketamine administration outlasted the period of anesthesia [6] and that this analgesic effect occurred even at subanesthetic doses of ketamine [7]. Subanesthetic doses of ketamine have been shown to be either potent analgesic in the postoperative period [8]. In mice, (+) ketamine was shown to be three times more potent than (-) ketamine as an analgesic, and 1.5 times more potent in terms of its hypnotic effects [9]. More importantly, at equianalgesic doses the (+) isomer caused less excitation than (-) ketamine. The dextrocetamine used in this study has been recently studied, resulting in lower hypnosis, greater analgesia without psychedelic effects compared to the racemic mixture [3]. In this study the incidence of dextroketamine produced a satisfactory analgesia (no pain) to needle insertion at 61.25% of patients and none of the 80 patients required more sedation (at a score of 4).

According to the manufacturer, lower doses of ketamine used in conjunction with diazepam may reduce the psychiatric manifestations during emergence [10]. This study used fixed-dose midazolam 1 mg, but not enough to avoid this unpleasant effect.

In a meta-analysis of over 8,000 pediatric sedation procedures in the emergency department involving ketamine, the frequency of emesis was 8.4% [11]. However, most episodes of ketamine-induced emesis are not severe, and patients can usually take liquids orally shortly after regaining consciousness [11]. In this study there was no emesis in any patient, but nausea occurred in 2 patients with the highest dose (0.25mg.kg^{-1}).

Emergence phenomena have been the most frequently reported adverse effects of ketamine. These reactions are described as a feeling of floating, vivid dreams, hallucinations, and delirium [12]. They appear to be related to the dose and rate of drug administration [13]. In our study, using dextrocetamine confirmed that the development of these effects was dose dependent.

Ketamine differs from most anesthetic agents in that it appears to stimulate the cardiovascular system, producing increases in heart rate, cardiac output, and blood pressure [14]. Benzodiazepines are reported to attenuate these effects [15]. In our study, we used fixed-dose midazolam (1 mg), and have had increased heart rate in 3 patients and systolic blood pressure in two patients, all with the two higher doses.

Ketamine has been used for a wide range of procedures, including preoperative and intraoperative sedation, single-agent anesthesia, balanced anesthesia, regional anesthesia, spinal anesthesia, and postoperative analgesia. Another reason for the renewed interest in ketamine is the availability of S (-) ketamine.

When studied at subanesthetic doses, its analgesic efficacy correlates well with its inhibiting action on NMDA receptor-mediated pain facilitation [16] and a decrease in activity of brain structures that respond to noxious stimuli [17].

Ketamine therefore represents a promising modality in several perioperative strategies to prevent pathologic pain. In this study, ketamine has been used to reduce or abolish pain during injection needle for spinal anesthesia with dose-dependent effect.

The authors investigated the psychotomimetic and cognitive effects of two subanesthetic doses of ketamine (0.1 mg.kg^{-1} and 0.5 mg.kg^{-1}) [18]. Ketamine caused impairments on all tests except immediate recall and the Mini-Mental State Examination. In our study, was not performed cognitive testing, but used four different doses, it was observed that the hallucination appearance was dose dependent.

At anesthetic doses of ketamine (i.e.,1–3 mg/kg), more than one third of patients may have unpleasant dreams or acute psychosis-like symptoms that may or may not be associated with hallucinations on emergence [19]. Subanesthetic doses of ketamine (0.1 mg.kg^{-1} or 0.5 mg.kg^{-1}) impair some domains of cognitive function, such as attention, free recall, recognition memory, and thought processes in healthy human volunteers [18, 20].

In recent study using three groups at doses of 0.3, 0.4 and 0.5 mg.kg^{-1} the authors have shown that ketamine produced dose dependent sedation with statistically significant difference among the three groups [21]. In our study using four different doses of dextrocetamine, all lower than the lowest dose in another study [21] obtained almost the same results. These authors concluded that the ketamine in the dose of 0.3 mg/kg provided sufficient sedation for allaying procedural discomfort due to less sedation, less positional difficulty, early verbal response, no hallucinations, no recall of performance of procedure and good patient satisfaction [21]. Practically we obtained the same results with lower doses.

Most patients fear pain or the possibility of pain during needle insertion for a spinal technique. Frequently needle insertion in the subarachnoid space in adult patients is performed with

sedation (benzodiazepines and opioids) and infiltration of the needle path with local anesthetic. Various drugs had been used to produce sedation for neuraxial block. In subanesthetic doses, ketamine possesses analgesic properties [22]. Ketamine at a dose of 0.1 $mg.kg^{-1}$ provides sufficient sedation to place the patient in position for spinal puncture and puncture pain relief in 50% of patients, without hemodynamic changes. The relief of pain and side effects are dose dependent.

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