Comparison of the Effects of Four Subdoses of Dextroketamine to Reduce Pain during Posterior Brachial Plexus Block: A Randomized Double Blind Study

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Abstract

Background: The needle puncture produces discomfort during regional anesthesia. Sedation and local anesthesia are used to promote analgesia and amnesia. The main objective of this study was to compare the efficacy of four subanesthetic doses of dextroketamine for pain relief during brachial plexus block via the posterior approach. Materials and Methods: Patients American Society of Anesthesiology I and II programed for elective surgery under brachial plexus block were distributed at randomized into four groups of twenty patients. Group A received dextroketamine 0.1 mg/kg, Group B received dextroketamine 0.15 mg/kg, Group C received dextroketamine 0.2 mg/kg, and Group D received dextroketamine 0.25 mg/kg. Sedation, facility to positioning, reaction to pinprick, nystagmus, hallucination, tachycardia, elevation of systolic blood pressure or cardiac rate, reduction in SpO2 (<96%), apnea, airway obstruction, collateral effects, and patient satisfaction were monitored. Results: There is a positive correlation between increasing dose of ketamine and the degree of sedation and easiness to position the patient on the table. There exists a negative correlation associated between increasing the dose of ketamine and the response to pinprick, as also to the incidence of hallucination. Conclusion: Dextroketamine in doses of 0.1 mg/kg provide sufficient sedation to maintain the patient in position for brachial plexus block and for the relief of pain in 55% of them during the procedure, without hemodynamic variation. The pain relief and collateral effects are dose-dependent.

Keywords: Brachial plexus block, ketamine, regional anesthesia, subanesthetic doses

Introduction

The brachial plexus block offers great benefits for surgery in the upper limbs. These benefits include major control of intraoperative pain, attenuation of the surgical response, minimal circulatory compromise, lesser incidence of nausea and vomit, excellent postoperative analgesia, reduced in-hospital stay and better cost-effectiveness budget, and lesser circulatory compromise.1 The discomfort during the procedure to provide peripheral block occurs even after preanesthetic evaluation and the use of a comfortable medication.

To proceed any regional block, it is necessary the insertion of a needle of a variety of gauge and tip design. It may be painful. To attenuate this problem and to improve the comfort to patients, sedation is induced to provide analgesia and amnesia.2 Infiltration of the puncture site with local anesthetic is necessary to provide pain relief and reduce the incidence of pain during peripheral block needle puncture.

Ketamine was introduced as a sole anesthetic agent with power to produce analgesia, amnesia, unconsciousness, and immobility. The isomer S(+) ketamine would provide lesser adverse effects such as nausea and vomit, as compared to the racemic mixture.3 Ketamine has a rapid, smooth, and previsible effect. In low doses, it has a fast action and previsible duration and produce a dissociative anesthesia with sedation, analgesia, and amnesia.4

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How to cite this article: Imbellon LE, Gouveia MA, de Morais Filho GB. Comparison of the effects of four subdoses of dextroketamine to reduce pain during posterior brachial plexus block: A randomized double blind study. Anesth Essays Res 2017;11:345-9.
The primary objective of this prospective study was to compare the efficacy of four subanesthetic doses of dextroketamine in the reduction of pain during the placement of a brachial plexus block through the posterior approach technique with the use of a needle of 30° bevel. Besides that, secondary effects of dextroketamine were also observed such as incidence of nystagmus, discrete hallucination, incidence of tachycardia, and high blood pressure, and satisfaction with the technique in the Postanesthetic Care Unit.

**Materials and Methods**

After registration of the protocol in the Plataforma Brasil (CAAE: 33373214.1.0000.5179) and approval of the Ethic Committee in Research (Register number 05787/2014) and the signature of approval to participate in the protocol, the double-blind study was applied in patients between 18 and 60 years of age, weighing between 50 and 90 kg of both sexes to undertake orthopedic surgery of the upper limb. Approved patients were of both sexes, included at random, physical status American Society of Anesthesiology I and II aged between 18 and 60 years weighing 50 and 90 kg candidates to orthopedic surgery of the upper limbs. Patients with cardiac and respiratory disease, mental illness, neurological disease, sensibility to local anesthetic, or coagulation disturbance were excluded from the study.

Utilizing the significant level of 5% and an error limit 0.10, the sample size was 62 patients. Eighteen more patients were added to totalize a sample of eighty patients in four groups of twenty patients. Patients were allocated in one of the four groups at random through a closed envelop. Group A received dextroketamine (Cristália Produtos Químicos e Farmacêuticos Ltda) 0.1 mg/kg, Group B received 0.15 mg/kg of dextroketamine, Group C received 0.2 mg/kg of dextroketamine, and Group D received 0.25 mg/kg of dextroketamine intravenously. After opening the envelope, the drug of the study was administered by an assistant through an insulin syringe.

No premedication was administered in the room. After venous puncture with 20 or 18G catheter was started, infusion of Ringer’s lactate solution began. Monitoring in the operating room consisted of continuous electrocardiogram using the CM5 lead, blood pressure by noninvasive method, and pulse oximetry.

After administration of midazolam (1 mg), sedation was evaluated[5] [Table 1]. After this evaluation, dextroketamine was administered according to the sorted group. Between 2 and 3 min after administration of dextroketamine, its effect was evaluated through the same sedation scale [Table 1]. The patient is placed in the sitting position for the administration of the block through the posterior access and facility or difficulty observed was noted. Patients were seated for the block to be placed. Facility or difficulty to place the patient in position for the block was noted according to a scale of two points: (1) The patient sits in the operating table without any help, (2) the patient needed help to sit up. With aseptic condition, the plexus block was performed with a Stimuplex® A100 needle gauge 21G with a cutting bevel of 30° (B. Braun Melsungen AG) without local anesthetic infiltration, coupled to a neurostimulator HNS12 (B. Braun Melsungen AG). The needle was advanced until a stimulus of the suprascapular nerve was excited with a stimulus of 0.5 mA and a response observed. After a negative aspiration for blood, 20 mL of lidocaine 2% (Cristália Produtos Químicos e Farmacêuticos Ltda) and 20 mL of Levobupivacaine 0.5% (Cristália Produtos Químicos e Farmacêuticos Ltda) were injected. A scale of four points was noted for the behavior of each patient during the introduction of the needle according to a four points scale [Table 2]. Following that, the patient was placed recumbent for the surgery. Nystagmus, hallucination, tachycardia, high blood pressure, high-frequency rate, high blood pressure, low blood O₂ saturation (<96%), apnea, airway obstruction, and any other collateral effects. The interval between ketamine injection and the final injection of the local anesthetic for the block through the posterior approach was noted.

**Statistical analysis**

The demographic profile was expressed as mean ± standard deviation. Hemodynamic parameters, SpO₂, respiratory frequency, and verbal response were evaluated through a nonparametric test of Kruskal–Wallis. Sedation score, positioning facility, and response to the needle introduction were compared through the Kruskal–Wallis test that is the nonparametric test for the ANOVA test. Hallucinations, nystagmus, and satisfaction of patients were evaluated through the chi-square test with the Monte Carlo simulation. A value of $P < 0.05$ was considered statistically significant.

**Results**

Demographic data were compared without no statistical difference between the four groups [Table 3]. The dose of 1 mg of midazolam produced score 1 of sedation in all patients, without significant difference.

| Table 1: Wilson sedation scale[6] |
|-----------------|------------------|
| 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 |
Maximal sedation (a score of 4) after the use of dextroketamine was not observed in any of the patients of the four groups. A score 3 was not observed in Group A, three patients were observed in Group B, five in Group C, and eight in Group D [Table 4]. There was a statistical difference between the sedation when a comparison between groups was established. Using the Spearman positive correlation was revealed between the increase of the dose and the grade of sedation ($r = 0.6069$).

Considering the positioning facility, in 18 patients of Group A, 15 patients of Group B, eight patients of Group C, and five patients of Group D positioned themselves, without any help [Table 5]. The easiness of positioning was significantly different among the groups. Using the Spearman correlation, it was revealed a positive relation between the increase of the dose of dextroketamine and the difficulty in positioning of the patient on the surgical table for the placement of the posterior brachial plexus block ($r = 0.5201$).

When the response to the first stitch was evaluated, 15 patients of Group D, 10 in Group C, 11 in Group B, and eight in Group A did not exhibit any movement [Table 6]. Using the Spearman correlation, a negative association was observed among the increase of the dose dextroketamine and the response to the needle stitch ($r = -0.1849$).

The Chi-square test with Monte Carlo simulation revealed a correlation between the increase in the dose of dextroketamine and hallucination ($C = 0.4543$, contingency coefficient). Utilizing the same test, there was not a correlation between the increase in the dose and the appearance of nystagmus [Table 7].

Among the eighty patients, only two in Group C and one in Group D were not satisfied with the method, justified by the appearance of hallucinations. Nausea did not occur in any of the eighty patients.

**Discussion**

In the present study, all patients that received subanesthetic doses of dextroketamine had a tendency to have a lower incidence of pain during the insertion of the needle for the placement of a posterior approach brachial plexus block. This study has also shown that sedation, the facility to position the patient, the reduction of needle pain, and the appearance of hallucinations was dose dependent. Different doses produced different results, but the time to proceed the block was the same for all four groups.

The available ketamine is a racemic balanced mixture of dextro and levo isomers. The dextro isomer is 3 times more potent as analgesic and 2–4 times more potent as analgesic, causing less psychedelic effects when compared to the levorotation or racemic form. The dextroketamine utilized in this study was recently studied, resulting in less hypnosis, greater analgesia, without psychedelic effects when compared to the racemic mixture. In this study, subanesthetic doses of dextroketamine produced satisfactory analgesia (no pain) during the insertion of the needle in 55% of patients and none of the patients presented a greater degree of sedation (score 4).

Lower doses of ketamine utilized associated with diazepam may reduce the psychiatric symptoms during the emergency of patients. In this study, midazolam was administered in

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**Table 3: Demographics data and the time to blockade (mean±standard deviation)**

| 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     |
|--------------------|-------------------|-------------------|-------------------|-------------------|-------|
| Age (years) (IQR)  | 36.95±13.72 (21.75) | 38.75±14.27 (15.75) | 35.22±12.10 (18.00) | 34.50±12.44 (18.25) | 0.7138*|
| Weight (kg) (IQR)  | 70.30±12.27 (7.00)  | 71.10±10.44 (12.25) | 68.33±9.25 (8.50)  | 65.90±8.40 (7.00)  | 0.3831*|
| Height (cm) (IQR)  | 167.20±10.44 (12.25) | 167.20±8.43 (6.25)  | 167.20±8.43 (6.25) | 167.25±10.96 (10)  | 0.6815*|
| Gender: Male/female| 18/2              | 18/2              | 17/3              | 15/5              | 0.5025'|
| Physical status: ASA (I/II) | 11/9          | 8/12              | 14/6              | 12/8              | 0.0801'|
| Time to block (min) (IQR) | 706±202 (0130) | 641±134 (058)   | 609±103 (0140) | 620±109 (143) | 0.3230*|

*Kruskal-Wallis, †Chi-square test with Monte Carlo simulation. ASA=American Society of Anesthesiology, IQR=Interquartile range

**Table 4: Score of sedation after dextroketamine 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     |
|----------------|-------------------|-------------------|-------------------|-------------------|-------|
| 1              | 20                | 12                | 6                 | 4                 | <0.001|
| 2              | 0                 | 5                 | 9                 | 6                 |       |
| 3              | 0                 | 3                 | 5                 | 10                |       |
| 4              | 0                 | 0                 | 0                 | 0                 |       |

**Table 5: Ease of positioning for plexus brachial block after dextroketamine 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     |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------|
| 1                 | 18                | 15                | 8                 | 5                 | <0.001|
| 2                 | 2                 | 5                 | 12                | 15                |       |
**Table 6: Score of response to block needle insertion**

| Score insertion 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  |
|------------------------|-------------------|--------------------|-------------------|-------------------|----|
| 0                      | 8                 | 11                 | 10                | 15                | 0.1784 |
| 1                      | 9                 | 8                  | 5                 | 3                 |    |
| 2                      | 2                 | 1                  | 4                 | 2                 |    |
| 3                      | 1                 | 0                  | 1                 | 0                 |    |
| 4                      | 0                 | 0                  | 0                 | 0                 |    |

**Table 7: Collateral effects of dextroketamine**

| Collateral 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  |
|--------------------|-------------------|--------------------|-------------------|-------------------|----|
| Nystagmus          | 9                 | 9                  | 14                | 12                | 0.1210 |
| Hallucinations     | 1                 | 2                  | 9                 | 11                | <0.0001 |

A fixed dose (1 mg) in all patients before the administration of dextroketamine, but it was not sufficient to prevent these uncomfortable effects. Many adverse effects are frequently related with the use of ketamine. These effects are described as floating sensation, vivid dreams, hallucinations, and delirium. They seem to be related to the dose administered. In our study, using low doses of dextroketamine, confirmed that the appearance of these effects was dose dependent.

Ketamine differs from the majority of anesthetic agents as they seem to stimulate the cardiovascular system, increasing the cardiac rhythm, cardiac debt, and blood pressure. Benzodiazepines are utilized to attenuate these effects. In our study, midazolam was used in a fixed dose of 1 mg, and an increase in cardiac beats was found in three patients (Groups C and D) and an increased blood pressure in two patients of the same group.

When used in subanesthetic doses, its analgesic efficacy correlates with its inhibitor action in the N-methyl-D-aspartate receptor and also a reduction of the activity of cerebral structures that respond to nociceptive stimuli. Ketamine represents, by all means, a promising modality in a variety of perioperative strategy to prevent pain. In this study, dextroketamine was utilized to reduce or abolish pain during the placing of a brachial plexus block by the posterior approach with a 21G needle, in a dose dependent effect.

With anesthetic doses of ketamine (that is, 1–3 mg/kg), more than one-third of patients may have unpleasant dreams or psychotic symptoms that may or not be associated with hallucination. Subanesthetic doses of ketamine (0.1 mg/kg or 0.5 mg/kg) may harm some areas or control of cognitive function, such as attention, free recall, memory of reconnaissance, and the process of thought, in healthy human volunteers. In our study, utilizing four different doses, no cognitive tests were realized, but we observed cases of hallucination that were dose dependent.

In a recent study evaluating spinal anesthesia with a 25G cutting needle, three groups with doses of 0.3, 0.4, and 0.5 mg/kg, the authors concluded that ketamine produced dose-dependent sedation with a statistical difference between the three groups. These authors concluded that ketamine in the dose of 0.3 mg/kg provided sufficient sedation to dissipate the discomfort due to a minor sedation, lesser difficulty to position for the block, short time for verbal response, no hallucinations, and patient satisfaction. In our study, utilizing four different doses of ketamine, all of them smaller than the smallest one in the other study, the same results were obtained.

Ketamine was used for a variety of procedures including preoperative and intraoperative sedation, anesthesia as a sole drug, balanced anesthesia, and sedation during regional anesthesia and postoperative analgesia. Another reason for the interest on this drug is the availability of the S(−) ketamine. The majority of patients fear the pain or the possibility of pain during the insertion of the needle for a regional technique. The insertion of the needle in an adult patient is conducted with prior sedation (benzodiazepine or opioid) and infiltration with local anesthetic.

**Conclusion**

In subanesthetic doses, ketamine has analgesic effects. Dextroketamine in doses of 0.1 mg/kg provided sufficient sedation to place the patient in a comfortable position to facilitate the administration of the block with 21G needle in 55% of patients, with no hemodynamic change. The pain relief and collateral effects are dose dependent.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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