Evaluation of Preemptive Effect of Epidural S(+)-Ketamine for Hysterectomy: Plasmatic Concentrations of Interleukins

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Background and objectives: Some studies showed that ketamine inhibits the production of cytokines. The objective of this study was to evaluate the preemptive analgesic effect of epidural S(+)-ketamine in hysterectomy and plasmatic cytokines (IL-6, TNF-α and IL-10).

Method: A double-blinded study with 29 patients was conducted. Patients in Group 1 received 13 mL of 0.25% bupivacaine with 25 mg of S(+) ketamine 30 minutes before surgical incision and 15 mL of saline solution via the epidural route 30 minutes after. Patients in Group 2 received 15 mL of saline solution 30 minutes before the surgical incision, followed by 13 mL of 0.25% bupivacaine with 25 mg of S(+) ketamine 30 minutes after. Postoperative analgesia was made with epidural bupivacaine and fentanyl. Dipyrone 1 g was used whenever required. The following parameters were evaluated: concentration of cytokines, intensity of pain, time of first request of analgesic and total quantity of analgesic used.

Results: Time for the first request for analgesics was 61.5 minutes in Group 1 and 69.0 in Group 2, without difference between these groups. There was no difference for total dose of fentanyl used in Group 1 (221.4 µg) and Group 2 (223.3 µg). A similar analgesic effect was obtained in both groups, except in T12 (Group 1 = 2.4 ± 3.2; Group 2 = 5.5 ± 3.4). No differences in concentration of cytokines were observed.

Conclusions: The epidural injection of 25 mg S(+) ketamine before incision reduced the pain intensity only 12 hours after surgical incision and did not alter concentration of cytokines.

Keywords: Ketamine; Analgesia; Anesthesia, Epidural; Cytokines; Hysterectomy.

INTRODUCTION

The stimulus of surgical trauma provokes peripheral and central sensitivity, with modification of neurons and resulting in allodynia, hyperalgesia and increase of postoperative pain intensity1. It also causes increase in the concentrations of cytokines 2,3.

Pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-8) indirectly modulate pain through the release of substances like nitric oxide, oxygen free radicals, prostaglandins, and excitatory amino acids from microglia and astrocytes, inducing peripheral and central sensitivity and hyperalgesia 4.

NMDA receptors have an important role in processing pain. The activation of these receptors by excitatory neurotransmitters, especially glutamate, is essential to the development of central sensitivity and amplification of pain response 1. Some drugs have been investigated to prevent or modify these alterations in the central nervous system. Ketamine is an antagonist of NMDA receptors and the S(+) ketamine isomer is more powerful than the racemic drug and causes less adverse effects 5-10. Although many studies have used ketamine, its preemptive effect is controversial 11-13. There is not much information available about administration of epidural ketamine and attenuation of inflammatory response. In a study, a low dose of epidural ketamine did not promote prevention of chronic pain after thoracotomy 14.

The objective of this study was to evaluate the preemptive analgesic effect and repercussions of epidural S(+) ketamine on plasmatic concentrations of IL-6, IL-10 and TNF-α in patients undergoing hysterectomy.

METHOD

A prospective, double-blinded, randomized study was conducted in 29 patients aged between 18 and 60 years, ASA physical status I or II, undergoing abdominal hysterectomy. The study obtained the approval by the Ethics Committee in Research and the patients signed the informed consent.
form. The exclusion criteria were the following: infection in the puncture site, coagulation disorders, hypertension, cancer, psychiatric, cardiac or hepatic disease and analgesic use in the week prior to surgery.

Patients were randomly divided into two groups. The investigator in charge of the evaluation did not know if the patient received the association of bupivacaine and S(+)-ketamine 30 minutes before or after the surgical incision until the end of study. A physician prepared the solution in the same volume and gave it to the anesthesiologist, who did not know its content.

Oral diazepam (10 mg) was administered one hour before the anesthesia. The epidural catheter was kept to control post-operative pain. General anesthesia was induced with propofol (2.5 mg.kg⁻¹) and intubation was carried out with rocuronium (0.5 mg.kg⁻¹). Anesthesia was kept with isoflurane/oxygen. Neither nitrous oxide nor opioids were administered.

Group 1 patients received 13 mL of 0.25% bupivacaine without vasoconstrictor via the epidural route associated with 25 mg of S(+)-ketamine in 2 mL of saline solution, 30 minutes before the surgical incision, followed by 15 mL of saline solution 30 minutes after. Group 2 patients received 15 mL of saline solution 30 minutes before the surgical incision, followed by 13 mL of 0.25% bupivacaine without vasoconstrictor, plus 25 mg of S(+)-ketamine in 2mL of saline solution 30 minutes after the surgical incision.

Blood samples were collected to measure cytokines on the following moments: before the surgical incision (M0), three (M3), six (M6), 12 (M12) and 24 hours (M24) after the surgical incision. Blood was collected on EDTA tubes and centrifuged at 3.000 rpm for 15 minutes. Plasma was stored at -70°C until the moment of analysis. Cytokine levels were determined by ELISA (PharMingen, EUA). All values were reported as picograms per milliliter. The variation coefficients of the im-

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EVALUATION OF PREEMPTIVE EFFECT OF EPIDURAL S(+) -KETAMINE FOR HYSTERECTOMY: PLASMATIC CONCENTRATIONS OF INTERLEUKINS

Table III – IL-6, IL-10 and TNF-α Concentrations (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>IL-6 (pg.mL⁻¹)</th>
<th>IL-10 (pg.mL⁻¹)</th>
<th>TNF-α (pg.mL⁻¹)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Group 1 (n = 14)</td>
<td>Group 2 (n = 15)</td>
<td>Group 1 (n = 14)</td>
</tr>
<tr>
<td>M₀</td>
<td>6.6 ± 12.9</td>
<td>7.2 ± 11.2</td>
<td>32.4 ± 58.6</td>
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<tr>
<td></td>
<td>(-0.9 – 14.0)</td>
<td>(0.8 – 13.7)</td>
<td>(-1.5 – 66.2)</td>
</tr>
<tr>
<td>M₃</td>
<td>36.7 ± 50.0</td>
<td>48.0 ± 57.3</td>
<td>45.0 ± 41.0</td>
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<td></td>
<td>(7.7 – 65.5)</td>
<td>(17.3 – 80.7)</td>
<td>(21.2 – 68.6)</td>
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<tr>
<td>M₆</td>
<td>53.3 ± 26.2</td>
<td>86.4 ± 64.7</td>
<td>41.1 ± 50.0</td>
</tr>
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<td></td>
<td>(28.4 – 56.7)</td>
<td>(50.6 – 122.2)</td>
<td>(12.2 – 70.0)</td>
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<tr>
<td>M₁₂</td>
<td>36.1 ± 28.1</td>
<td>48.5 ± 34.3</td>
<td>90.0 ± 144.7</td>
</tr>
<tr>
<td></td>
<td>(19.9 – 52.4)</td>
<td>(29.6 – 67.5)</td>
<td>(10.0 – 170.2)</td>
</tr>
<tr>
<td>M₂₄</td>
<td>30.9 ± 27.2</td>
<td>33.2 ± 18.0</td>
<td>34.5 ± 47.4</td>
</tr>
<tr>
<td></td>
<td>(15.2 – 46.6)</td>
<td>(12.3 – 43.1)</td>
<td>(7.2 – 62.0)</td>
</tr>
</tbody>
</table>

Group 1: before incision; Group 2: after incision. M₀: before incision. M₀, M₃, M₆, M₁₂, M₂₄: 3, 6, 12, and 24 h after surgical incision; without statistic difference between groups, Mann-Whitney test.

DISCUSSION

Hysterectomy was chosen because this procedure provokes intense pain stimulus during the postoperative period and afferent stimulus may be blocked with epidural drugs. The duration of surgery was similar in both groups and, therefore, the time for evaluation of the patient was also similar. General anesthesia was maintained with agents that do not have preemptive analgesic effect. A patient was excluded from Group 1 because she received a drug that was not allowed according to the protocol.

In the present study there was no reduction of intensity of postoperative pain with epidural infusion of S(+) -ketamine and bupivacaine before surgery when compared with the same injection administered after the beginning of the surgical stimulus. Even though a significant difference in pain scores was not observed and the number of patients was small, the score was lower in Group 1 in all evaluated moments. Those data lead us to mention a tendency for improved analgesia when the solution was administered before the surgical incision. At M₁₂, pain intensity was lower in Group 1 than in Group 2, which confirms this tendency, but is not enough to support a preemptive effect.

An analgesic effect was not obtained despite the epidural administration of drugs being considered efficient to reduce intensity of acute postoperative pain 14. The epidural solution consisted of a combination of a local anesthetic and S(+) -ketamine because these drugs work through different mechanisms with more intense analgesic effect. The volume of the analgesic solution may have been insufficient to prevent alterations in the central nervous system resulting from the deleterious stimulus generated by the surgery.

General anesthesia was maintained with agents that do not have preemptive analgesic effect. Although there are many studies investigating preemptive analgesia, the methods employed by most researchers are considered inappropriate. Many studies were not double-blinded or patients were not randomized. In other studies, patients did not receive the same analgesia before and after the surgical incision 15,16, or the analgesic was compared with saline solution administered before the surgical incision 15, rendering an inaccurate evaluation. In addition to that, researchers did not consider the sensitivity induced by the inflammatory response within the immediate postoperative period 16,17.

A protocol of preemptive analgesia suggested by McQuay was used in this study, in which the effect on postoperative pain is observed with the drug administered before and after surgical incision in the same dose and by the same route 18.

A systematic review concluded that the preemptive analgesic effect depends on the selected analgesic technique. One study demonstrated an evident preemptive effect with epidural analgesia, reducing pain intensity and consumption of complementary analgesics, thus increasing the time to request the first complementation 19. Other authors also obtained reduction of intensity of postoperative pain by administering ketamine before and during surgery 20,21. Nevertheless, they did not obtain an improved analgesic effect with ketamine when administered before incision or after surgery 22,23.

Antagonists of NMDA receptors like ketamine may reduce central sensitivity and hyperalgesia 3,7-10,24. Ketamine could be effective to attenuate cytokines during surgery and improve recovery 15,25.

This study investigated pro-inflammatory (IL-6, TNF-α) and anti-inflammatory (IL-10) cytokines to check their concentrations with trauma and epidural drugs. Concentrations of interleukins were evaluated 3 hours after surgical incision, since production of cytokines is observed within 2-4 hours after tissue injury 26. Epidural S(+) -ketamine before or after surgical incision did not promote different plasmatic concentrations of IL-6, TNF-α or IL-10. However, IL-6 and IL-10 levels were significantly lower in Group 1 in almost all moments.

Finally, the epidural injection of 25 mg of S(+) -ketamine before the incision reduced the pain intensity only 12 hours after surgery and did not alter the production of cytokines. The maintenance of S(+) -ketamine during postoperative period seems to be an interesting proposal to be tested.
AVALIAÇÃO DO EFEITO PREEMPTIVO DA S(+)-CETAMINA POR VIA PERIDURAL PARA HISTERECTOMIA: CONCENTRAÇÕES PLASMÁTICAS DE INTERLEUCINAS

REFERÊNCIAS / REFERENCES