

Evaluation of ketorolac compared to ketorolac plus dipyrone in post-operative analgesia of videolaparoscopic cholecystectomy

Avaliação do efeito da dipirona associada ao ceterolaco comparado ao ceterolaco em pós-operatório de colecistectomia videolaparoscópica

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ABSTRACT

Objectives: To compare the analgesic effect of ketorolac with the association of ketorolac plus dipyrone after videolaparoscopic cholecystectomy and with a placebo group. **Methods:** After approval by the Research Ethics Committee and after having the informed consent signed, 60 patients aged between 18 and 60 years who underwent videolaparoscopic cholecystectomy were evaluated for the post-operative analgesia provided by ketorolac compared to ketorolac plus dipyrone. The patients underwent general anesthesia (with propofol, alfentanil, rocuronium and maintenance with isoflurane). Twenty patients received 20 ml water, 20 patients received ketorolac 30 mg in 20 ml water and 20 received ketorolac 30 mg plus dipyrone 2 g in 20 ml water, during anesthetic induction. In the post-operative recovery room, the patients were evaluated to the moment of their first pain complaint with the use of a visual analogue scale and a verbal pain scale every hour in the first six hours. When necessary, morphine was administered as a rescue medication for pain relief and a PCA pump with morphine solution was turned on. **Results:** Total morphine use was lower in the ketorolac plus dipyrone Group (2 mg) and in the ketorolac (2 mg) Group, compared to the placebo Group (10.5 mg). Of 20 cases of ketorolac plus dipyrone, eight patients did not complain of pain in the post-operative period, while only three patients did not complain in the ketorolac Group and in the placebo Group ($p = 0,05$). **Conclusion:** Ketorolac is a potent analgesic agent widely used for acute pain treatment, especially after surgeries, with an analgesic potency comparable to that of opiates, the most commonly drugs used during the post-operative of medium to major surgeries. In this study, the results analyzed at this moment show that the association of ketorolac plus dipyrone seemed to be superior to post-operative analgesia compared to the use of ketorolac.

Keywords: Cholecystectomy, laparoscopic; Ketorolac; Dipyrone; Drug interactions

RESUMO

Objetivos: Comparar o efeito analgésico do ceterolaco e da associação ceterolaco mais dipirona após cirurgias de colecistectomias videolaparoscópicas. **Métodos:** Após a aprovação do Comitê de Ética e a obtenção do consentimento informado, 60 pacientes com idade entre 18 a 60 anos e candidatos à colecistectomia videolaparoscópica, foram submetidos ao procedimento cirúrgico sob anestesia geral balanceada com propofol, alfentanil, rocurônio e manutenção com isoflurano. Foram divididos em três grupos: placebo, recebendo 20 ml de solução salina; ceterolaco com 30 mg de ceterolaco em 20 ml de solução salina; e ceterolaco mais dipirona, recebendo 30 mg de ceterolaco e 2 g de dipirona em 20 ml de solução salina. Os fármacos foram aplicados por via venosa, no início da incisão cirúrgica. Na sala de recuperação pós-anestésica os pacientes foram avaliados, quanto ao momento da primeira queixa dolorosa pela escala visual analógica e verbal e grau de sedação, a cada hora nas primeiras seis horas. Se necessário era utilizada como medicação de resgate, morfina administrada por bomba de analgesia controlada pelo paciente. **Resultados:** O consumo total de morfina no pós-operatório foi menor no Grupo ceterolaco mais dipirona (2 mg) e no Grupo ceterolaco (2 mg) comparado ao Grupo placebo (10,5 mg) com $p = 0,10$. No Grupo ceterolaco mais dipirona, oito pacientes não referiram dor no pós-operatório, enquanto que apenas três no Grupo ceterolaco e três no Grupo placebo não se queixaram de dor ($p = 0,05$, teste do χ^2). **Conclusão:** O ceterolaco tem sido amplamente utilizado no tratamento da dor aguda, especialmente a pós-operatória, principalmente em cirurgias de médio e grande porte, isoladas ou associadas aos opioides. No presente estudo, a associação de ceterolaco com dipirona se mostrou superior na analgesia após colecistectomias videolaparoscópicas quando comparada ao ceterolaco.

Descritores: Colecistectomia laparoscópica; Ceterolaco; Dipirona; Interações de medicamentos

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INTRODUCTION

Dipyron is a non-opioid analgesic and antipyretic belonging to the class of non-steroid anti-inflammatory drugs (NSAID). This drug is used in countries in South America and in some European countries, such as Germany, Italy and Spain. Dipyron has proved to be a very effective analgesic. When administered in equipotent doses, its effect is compared to that of several opioids, such as tramadol. In addition to its analgesic effect, it is also antipyretic and antispasmodic and has no anticholinergic effect⁽¹⁾.

NSAIDs are important drugs for the treatment of pain and they have been widely used for pain control. Most NSAID have anti-inflammatory, antipyretic, antiplatelet and analgesic effects, although the proportion of each effect depends on the drug used. These effects are related to the inhibition of the enzyme cyclooxygenase, which is responsible for converting arachidonic acid into prostaglandin, prostacyclins and thromboxanes, all playing a fundamental role in inflammation caused by tissue injury⁽²⁾.

There are two distinct types of this enzyme: COX-1 and COX-2⁽³⁾. COX-1 is constitutive and synthesizes prostanoids responsible for maintaining normal organ functions, such as the kidneys, gastrointestinal mucosa, platelets and vascular endothelium. COX-2 is inducible at the sites of tissue insult, but in some tissues, such as the central nervous system, reproductive organs and placenta, it is expressed in a constitutive mode and shows physiological properties⁽⁴⁾. COX-2 is rapidly expressed in the presence of distinct inflammatory stimuli, thus mediating the pain, inflammation, fever and local vasodilation⁽⁵⁾.

The analgesic properties of NSAID are due to COX-2 blockade and most side effects are a consequence of the COX-1 blockade, especially hemorrhagic gastritis. The association of NSAID and morphine has an addition effect, causing a reduction by 20 to 40% in the use of opioids in the immediate post-operative period of medium and major surgeries, resulting in less adverse effects caused by opioids and NSAID.

Ketorolac tromethamine is a non-selective NSAID that acts indistinctly on COX-1 and COX-2, and it is used in the treatment of post-operative pain of moderate or severe intensity⁽⁶⁻⁹⁾. Its main usefulness in post-operative analgesia is intravenous use. The most common adverse effects reported with ketorolac, when used as a single dose, include drowsiness, nausea, vomiting and dry mouth, but with no significant difference when compared to placebo⁽¹⁰⁾. Better analgesia was shown with the combination of ketorolac and paracetamol, when compared to the isolated use of ketorolac as to tolerance to pain⁽¹¹⁾.

OBJECTIVE

To evaluate the analgesic efficacy of dipyron associated with ketorolac, compared to the isolated use of ketorolac in the first six hours of the post-operative period of videolaparoscopic cholecystectomy.

METHODS

After approval by the Research Ethics Committee, a total of 60 patients of both genders, ages between 18 and 60 years and with a surgical indication of videolaparoscopic cholecystectomy, were prospectively studied. After clarification and signature of the informed consent term, the patients were randomly assigned to three groups.

Anesthetic technique

The surgical procedure was performed under general anesthesia with orotracheal intubation. Venopuncture with a 20 G catheter was carried out in an upper limb; anesthesia was induced and maintained with propofol 100 to 200 mg, alfentanil (initial dose of 50 $\mu\text{g}/\text{kg}$; maintenance dose of 1 $\mu\text{g}/\text{kg}/\text{minute}$) and rocuronium 0.6 mg/kg. Supplemental doses of rocuronium were administered whenever neuromuscular relaxation was required.

During the procedure, the patients were maintained under controlled ventilation with a mixture of oxygen in compressed air and a FiO_2 of 50%, and isoflurane at a concentration of 0.5 to 1 MAC. The following parameters were monitored: non-invasive blood pressure by oscillometry, continuous pulse oximetry, continuous ECG in DII lead, analysis of exhaled CO_2 and respiratory rate by capnography. Patients in Group I received dipyron 2 g plus ketorolac 30 mg, in a volume of 20 ml through intravenous administration at the beginning of surgical incision. Patients in Group II received ketorolac in a volume of 20 ml through intravenous administration at the beginning of surgical incision. Patients in Group III received 0.9% saline solution in a volume of 20 ml through intravenous administration at the beginning of surgical incision. Administration of these solutions was carried out by a researcher who did not participate in the assessment of pain and adverse effects. At the end of the procedure, the patients were sent to the post-anesthetic recovery room (PARR).

Evaluation and treatment of post-operative pain

At the PARR, the patients were periodically evaluated for six hours in regard to pain intensity in the surgical

incision and abdominal region, from the moment of the first complaint of pain, with a visual numeric scale (VNS) and a categorized verbal evaluation scale of five scores (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = intense pain; 4 = worst possible pain). When the patient presented a pain score ≥ 3 at the VNS or a score of 2 at the verbal scale, the said patient was treated with a 2 mg morphine bolus every five minutes until reduction to a VNS score < 3 or a verbal scale score ≤ 1 , or respiratory rate < 8 . After achieving one of these parameters, the PCA pump was set with a morphine solution 1 mg/ml, for administration of 1 mg morphine bolus with a minimum interval of five minutes.

The time interval between arousal and the first pain complaint was recorded as well as the amount of morphine used until pain relief and the total amount used in six hours. Pain evaluation with the visual analogue scale and verbal scales was carried out every hour, as well as the observation of adverse events. Patients were evaluated for six hours, starting from the first complaint of pain, when the observation period was finished, and those patients were sent to their original wards. Prescription of analgesics after the PARR stay was at the discretion of the surgical team.

The Mann-Whitney test allowed the comparison between groups, while the ANOVA test of repeated measurements followed by the Friedman test allowed us to observe the differences between the evaluation times in the same group. Demographic data were evaluated by the Kruskal-Wallis test.

RESULTS

Population data of the three groups treated were analyzed with the Kruskal-Wallis test (age: $p = 0.394$) with no statistically significant difference between the groups.

The time elapsed until the first pain complaint was not significantly shorter in the group treated with ketorolac (69 minutes) and in the group treated with ketorolac plus dipyrone (55 minutes) when compared to the Control Group (37.5 minutes), but it tends to be longer than in the Control Group ($p = 0.12$).

The mean values of morphine dose necessary for pain relief were 2 mg in the ketorolac Group, 2 mg in the ketorolac plus dipyrone Group and 10.5 mg in the control Group ($p < 0.001$).

When the groups are isolated and compared in regard to the morphine use, the control Group needs higher doses of morphine compared to the ketorolac Group ($p < 0.01$). The control Group also required higher doses of morphine when compared to the ketorolac plus dipyrone ($p < 0.01$) Group. However, the association between the ketorolac Group and the ketorolac plus

dipyrone Group did not show a statistically significant difference in regard to the amount of morphine used.

DISCUSSION

Pain is defined as an unpleasant sensory and emotional experience; however, until few decades ago it was considered an inevitable consequence of tissue injury inherent to a surgical procedure.

Acute pain affects millions of people all over the world every day, but only in recent years developments were accomplished for understanding the mechanisms inherent to the pain process and the treatment of people complaining of pain. These developments included new concepts in the management and treatment of post-operative acute pain, and comprised, unless contraindicated, the use of non-steroid anti-inflammatory analgesics.

Despite these developments, control and treatment of acute pain are frequently inadequate, especially in the post-operative period, when several patients suffer and have their recovery compromised by the unrelenting painful status.

Ketorolac tromethamine is a potent NSAID analgesic and is widely used in the treatment of acute pain, especially post-operative pain with an analgesic potency comparable to drugs generally used in the post-operative of medium and major surgeries, such as the opioids⁽¹²⁾.

Dipyrone is a simple analgesic widely used in Brazil. Soltesz et al. showed that the use of dipyrone 1 g four times a day after hysterectomy had an analgesic power comparable to that of parecoxib 40 mg twice daily⁽¹³⁾. This study evaluated the association of ketorolac and dipyrone for post-operative analgesia and no statistically significant difference was found compared to the isolated use of ketorolac.

In this study, the results presented were quite satisfactory in regard to the post-operative analgesia, since the ketorolac Group showed lower values of pain intensity obtained through the assessment methods, longer time elapsed until the first complaint of pain and decreased use of rescue morphine and total dose in six hours as recorded by the PCA pump. In this method, patients are able to control, in an individualized manner, their own analgesia.

There may have been a bias in the study since the surgeries evaluated are not rated as highly associated with pain, thus showing that ketorolac is equally efficient as the association of ketorolac and dipyrone.

These results ratify the effects expected with the use of NSAID, either the more efficient post-operative analgesia through multiple approaches to pain and the opioid-sparing effect, thus improving the quality of

post-operative recovery and decreasing the incidence of unwanted side effects inherent to the use of high doses of opioids^(3,10-11,14-16).

No significant side effects were seen during patient observation, although no specific methods were used.

CONCLUSION

The results of this study showed the efficacy of ketorolac as monotherapy, and in agreement with other studies, make ketorolac an important alternative to the treatment and control of post-operative pain. The association of ketorolac and dipyrrone is also a good alternative for post-operative analgesia. Further studies are necessary to show the analgesic efficacy of dipyrrone isolatedly and possible enhancement of the effect of NSAID with its use.

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