

# Efficacy of scheduled time ketorolac administration compared to continuous infusion for post-operative pain after abdominal surgery

A. RUSSO<sup>1</sup>, E. DI STASIO<sup>2</sup>, F. BEVILACQUA<sup>1</sup>, S. CAFAROTTI<sup>3</sup>,  
A. SCARANO<sup>1</sup>, E. MARANA<sup>1</sup>

<sup>1</sup>Department of Anaesthesiology and Intensive Care Medicine,

<sup>2</sup>Institute of Biochemistry and Clinical Biochemistry, and <sup>3</sup>Division of Thoracic Surgery; School of Medicine, Catholic University of the Sacred Heart, Rome, Italy

**Abstract. – BACKGROUND:** Ketorolac tromethanime is a non steroidal anti inflammatory drug and its efficacy on acute pain control after abdominal surgery has been well documented. It has a rapid onset and it can be given both for intra operative and for post operative pain management.

**AIM:** In this study we aimed to evaluate if there were any differences in relieving post operative pain when Ketorolac was administered with continuous infusion or if it was given at prearranged times.

**PATIENTS AND METHODS:** 80 ASA I patients, scheduled for major gynecological surgery, were randomly assigned to 2 groups: group A patients were connected after surgical incision with a 24h analgesic infusor (2 ml/h) containing morphine (0.02 mg/kg/h) and Ketorolac (90 mg). Group B patients were connected after surgical incision with a 24h analgesic infusor (2 ml/h) containing morphine (0.02 mg/kg/h) at first and Ketorolac was then given in bolus after surgical incision and then every 8 hours for the first 24 hours.

Post-operative pain scores were assessed using the Visual Analogue Scale (VAS) every 8 hours for 24 h. For a VAS value greater than 6, patients received Tramadol 100 mg.

**RESULTS:** Post-operative pain scores showed a better pain relief for patients in the group B. Furthermore, the requirements of rescue analgesic were less in the group B [Tramadol was used for only 8 patients] than in the group A [Tramadol was used for 31 patients]. No adverse effects were registered in both groups.

**CONCLUSIONS:** For post-operative pain Ketorolac administration at prearranged times, every 8 hours, offers greater benefits in respect to its continuous infusion.

*Key Words:*

Ketorolac, Post operative pain, VAS score.

## Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have become popular for pain relief after surgery. Ketorolac tromethanime is a non steroidal anti inflammatory drug that inhibits both cyclo-oxygenase and lipo-oxygenase enzymes, thereby, preventing the synthesis of both prostaglandins and leukotrienes<sup>1</sup>, and may also release endogenous opioids<sup>2</sup>. These properties of ketorolac may make it more potent than other NSAIDs. Its analgesic efficacy has been studied extensively for the treatment of pain in many clinical settings. After major abdominal, orthopedic or gynecological surgery or ambulatory laparoscopic or gynecological procedures, ketorolac provides relief from mild to severe pain<sup>3</sup>. It is available in both oral and parental forms. Injectable ketorolac is primarily used in intramuscular administration; however, it has also been reported the intravenous administration<sup>4-7</sup>. Ready et al<sup>8</sup> have demonstrated that intravenous ketorolac administered to middle-aged patients after general, gynecologic, or orthopedic surgery was equally effective when administered either as a continuous infusion or as intermittent boluses. Both methods were well tolerated and were associated with a 25% reduction in morphine consumption and lower pain scores compared to placebo.

The role of adjunctive NSAIDs for patients after abdominal or gynecologic surgery is controversial, since not all studies reported significant benefits<sup>9</sup>. In contrast, the analgesic efficacy of NSAIDs in major orthopedic surgery is well documented. Ketorolac is proved to be a safe alternative drug providing equivalent analgesia to opioids without

opioids-related adverse effects for post-operative analgesia in children<sup>10,11</sup> and has already been used in children undergoing urological surgery<sup>12,13</sup>. Park et al<sup>14</sup> reported that Ketorolac, as a cyclooxygenase inhibitor, can reduce the frequency and severity of bladder spasms after intravesical ureteroneocystostomy. Preventive analgesia using non-opioid analgesic strategies is recognized as a way to improve postoperative pain control while minimizing opioid-related side effects. Ketorolac is frequently used, but the optimal dose and means of administration for systemic single dose Ketorolac in preventing postoperative pain is not well defined. De Oliveira et al<sup>15</sup> performed a quantitative systematic review to evaluate the efficacy of a single dose of perioperative ketorolac on postoperative analgesia. It showed that single dose systemic Ketorolac is an effective adjunct in multimodal regimens to reduce postoperative pain. Improved postoperative analgesia achieved with Ketorolac also lead to a reduction in postoperative nausea and vomiting. The 60 mg dose offers significant benefits but there is a lack of current evidence providing that the 30 mg dose offers significant benefits on post-operative pain outcomes.

Due to these conflicting results, in the present study we aimed to evaluate if there were differences in post operative pain control when administering Ketorolac either in continuous infusion, or in boluses.

### Materials and Methods

This study received approval by our Institute and Ethical Committee of Catholic University of Rome, Italy. Each patient gave signed informed consent before inclusion.

We studied eighty ASA I women, 30-50 yrs of age, scheduled for elective gynecological surgery. Patients were enrolled if they had to undergo laparotomic hysterectomy.

Exclusion criteria included obesity (body mass index > 30 kg/m<sup>2</sup>), cardiac and respiratory diseases, renal impairment, liver disorders and allergies to any of the drugs used in this study.

Electrocardiogram, basal temperature, pulse oximetry (SpO<sub>2</sub>), non-invasive blood pressure (NIBP), and end tidal carbon dioxide concentrations (EtCO<sub>2</sub>) were monitored during anaesthesia. Bispectral index values (BIS) were monitored and maintained between 40-60 in order to reduce the occurrence of intra operative awareness.

General anaesthesia was standardized for all subjects. During induction, patients received Fentanyl (4 mcg/kg), Propofol (2 mg/kg), and Vecuronium (0.1 mg/kg). After intubation, anaesthesia was maintained with a mixture of oxygen (40% O<sub>2</sub>), air and sevoflurane (2-2.2%). Fentanyl was given in bolus so that heart rate and blood pressure did not exceed more than 15% from the basal values. Volume controlled ventilation was used and adjusted to maintain a normal range of expired CO<sub>2</sub> (i.e. 35-40 mmHg).

After intubation, a urinary catheter was inserted, and urinary output was monitored throughout the 24 hours of the study.

Fluid management was 10 ml/kg/h, using both crystalloids and colloids as necessary during surgery.

Patients were randomly allocated in two groups. In the Ketorolac continuous infusion group (Group A), patients were connected after surgical incision to a 24h analgesic infusor (2 ml/h) containing morphine (0.02 mg/kg/h) and ketorolac (90 mg). In the Ketorolac bolus group (Group B), patients were connected after surgical incision to a 24h analgesic infusor (2 ml/h) containing morphine (0.02 mg/kg/h); and then, Ketorolac was given in bolus after the end of surgery and every 8 hours for the first 24 hours (Table I).

Post-operative pain scores were assessed using a 100 mm Visual Analogue Scale (VAS) at rest and after coughing every 8 hours for 24 hours.

**Table I.** Demographic data and operating times of the population under study. Group A: Ketorolac continuous infusion group. Group B: Ketorolac bolus group.

	Group A (n = 38)	Group B (n = 37)	p
ASA	I	I	
Age (yrs)	38.4 ± 4.2	37.0 ± 3.5	> 0.05
Body weight (kg)	56.8 ± 8.7	60.3 ± 9.5	> 0.05
BMI	23.6 ± 1.0	22.8 ± 1.3	> 0.05
Operating time (min)	67 ± 12	69 ± 10	> 0.05
Bispectral index values (BIS)	47 ± 5	49 ± 6	> 0.05

We asked each patient to answer the following question (by placement of a slash mark): “How much pain do you feel from 0 to 10?” (evaluating: 0 as no pain at all, 1-2 mild pain intensity, 3-5 moderate pain intensity, 6-8 severe pain intensity, 9-10 worst pain ever felt). We divided patients in two groups: patients with a pain score < 6, and patients with a pain level > 6. Patients with VAS value higher than of 6 received Tramadol (100 mg i.v.). At the same times of VAS we also used the Ramsay sedation scale<sup>16</sup> (RSS).

With the RSS we wanted to assess the level of sedation of our patients throughout the 24 hours of the study. We evaluated: 1: anxious, agitated or restless, 2: oriented, calm and co-operative, 3: responsive to commands only, 4: exhibiting brisk response to light glabellar tap or loud auditory stimulus, 5: exhibiting a sluggish response to light glabellar tap or loud auditory stimulus, 6: unresponsive.

Furthermore, we registered adverse effects such as: nausea, vomiting, pruritus and ventilator depression.

### Statistical Analysis

Statistical analysis was performed by using the Statistical Package for Social Science (SPSS), release 15.0 (SPSS Inc., Chicago, IL, USA). The VAS score was expressed as median and range.

The statistical difference of frequency of patients with VAS higher or lower than six in Group A and B was calculated using the  $\chi^2$  test. The statistical significance was set at  $p < 0.05$ .

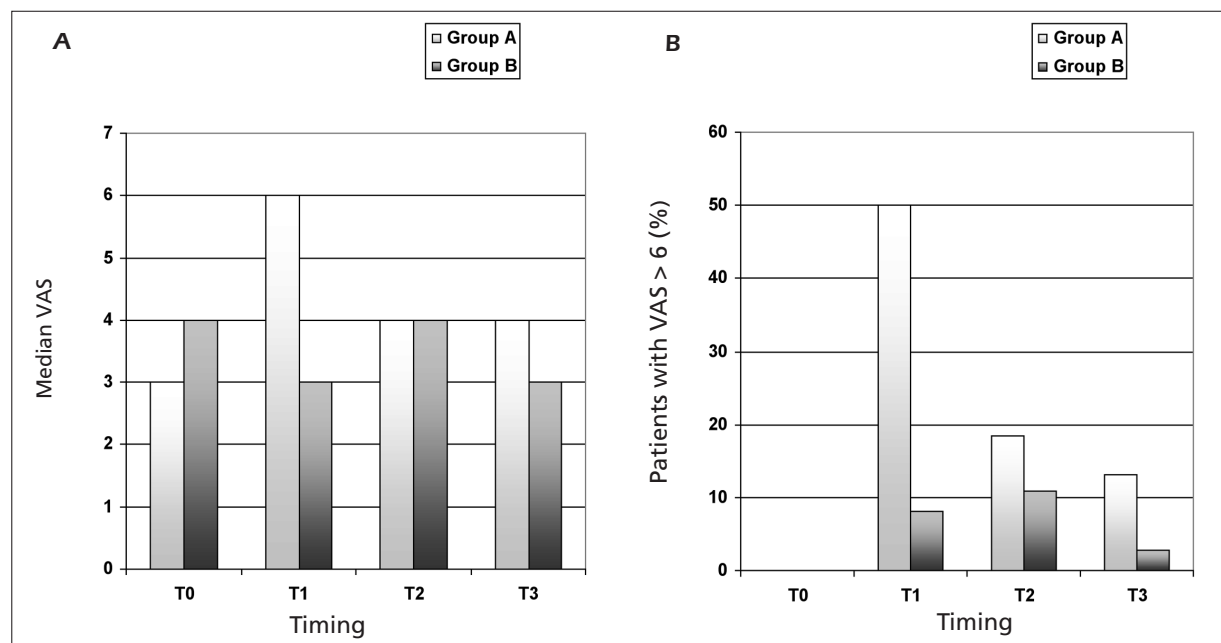
### Results

80 patients were enrolled in this study. Of these, five did not complete the 24 hours observation period. Two patients belonged to the continuous infusion group, and were excluded from the protocol for a technical reason (interrupted infusion for analgesic infusor failure).

Three patients from the bolus group were withdrawn: one patient because she took another NSAIDs (Ibuprofen instead of Ketorolac), another was excluded because of lack of analgesic efficacy, and the last one was excluded due to analgesic infusor failure.

All surgeries lasted  $70 \pm 15$  minutes. The evolution of pain intensity was measured 30 minutes after the end of surgery (T0), and every 8 hours from the end of anesthetic procedures, for the first 24 hours (T1, T2 and T3 respectively).

As showed in Figure 1, panel b), at T0 Tramadol was not necessary in both groups, because our patients did not feel enough pain to require a rescue analgesic.



**Figure 1.** **A**, Shows differences of median VAS grade of both groups at each time. **B**, Shows differences in number of patients who reported VAS scores higher than 6 (%) at each time. Group A: Ketorolac continuous infusion group Group B: Ketorolac bolus group.

We observed a higher value of median VAS in group A, with respect to group B at T1.

50% of group A patients had a VAS score > 6 and required Tramadol. This percentage was much higher with respect to group B at T1 (8%).

At the same time, as can be seen in Figure 1, panel a, median VAS value was 6 in group A, and just 3 in group B. These results are statistically significant, showing that in patients receiving Ketorolac continuous infusion pain was not managed as necessary during post operative.

Panel a) also shows that at T2 the median VAS was the same<sup>4</sup> in both groups, but as documented in panel b), Tramadol was given to 18% of group A patients, and to 11% of group B.

Results at T3 were quite similar to those at T2. Median VAS was 4 in group A, and 3 in group B. However, at this time, 14% of Ketorolac continuous infusion group patients required Tramadol due to a VAS score higher than 6.

The total frequency of patients that required Tramadol administration was 31 out of 38 and 8 out of 37 subjects belonging to groups A and B, respectively. The Odds Ratio of group A patients asking for more pain killer was 16.0 [5.2-49.9] ( $p < 0.001$ ) compared to group B.

The RSS measured at prearranged times did not show significant changes among groups at any time.

During all the 24 hours of the study, respiratory rate and oxygen saturation were measured in all patients, and no clinically significant changes were found. There were no statistical differences between groups regarding patients reporting post-operative nausea or vomiting, even if it was higher in the Ketorolac continuous infusion group, where patients assumed Tramadol. In these cases, nausea and vomiting were effectively treated with metoclopramide.

## Discussion

Ketorolac is a parenteral non-steroidal anti-inflammatory drug (NSAID) widely used for intra-operative and post-operative pain management.

Several studies focused on the efficacy of Ketorolac in combination with opioids (especially morphine)<sup>17</sup> and it is well documented that patients receiving Ketorolac during post operative required a lower amount of morphine using a patient-controlled analgesia (PCA)<sup>8</sup>. Furthermore, Jo et al<sup>18</sup> showed that intermittent Ketorolac administration with a low-infusion rate can be used to improve post-operative analgesia.

However, the reduction in opioid use was not statistically significant in all the studies that allocated patients in a Ketorolac continuous infusion group and in a Ketorolac bolus group. In fact Etches et al<sup>19</sup> reported that there were no differences in analgesia if Ketorolac was administered intra venous with continuous or intermittent infusion. Burns et al<sup>20</sup>, instead, found that there was great morphine sparing if Ketorolac was given in continuous infusion by intra muscular route.

Due to all these conflicting results, the purpose of the present study was to try to understand if there is a clinical benefit if Ketorolac is administered by boluses at scheduled times or by continuous infusion.

The reason why we found that Ketorolac in bolus led to a better pain relief could be related to its pharmacokinetic.

The Food and Drug Administration (FDA) reports that in adults, the bioavailability following administration of the oral or the IM form of Ketorolac, was equal to that following an i.v. bolus.

Ketorolac has a half-life for absorption of 3.8 min after oral and intramuscular administration<sup>21</sup>. The plasma elimination half-life is about 5 or 6 hours. In their study, Cohen et al<sup>22</sup> observed that if Ketorolac is given with continuous infusion, its plasma levels decrease progressively and at 4 and 6 hours after the dose, Ketorolac levels are lower than  $Ec_{50}$  in 50% and 71% of the population they studied, respectively. Several studies<sup>22,23</sup> showed that more than 96% of Ketorolac related material circulating is the parenteral drug, since it undergoes a minimal metabolism. Half maximal effect for analgesia in adults is 0.37 mcg/ml<sup>23</sup>.

In our investigation all patients received morphine during the first 24 hours of post operative, in order to guarantee a basal pain relief. Tramadol was then administered only if VAS score was higher than 6.

We did not find significant opioids side effects such as desaturation ( $SpO_2$  lower than 90%) or higher levels of sedation (RSS > 2).

Regarding Ketorolac's most frequent side effect, there were no differences between groups about post-operative blood loss.

Even if we didn't include in the study patients with renal impairment, we also did not assess renal function, which should be considered, especially for elderly patients.

Thanks to the short term Ketorolac administration (24 hours only) no gastrointestinal side effects such as bleeding or peptic ulceration were reported.

## Conclusions

Our study reported a better analgesia with Ketorolac administration at regular intervals (i.e. 8 hours) with respect to its continuous infusion.

## References

- 1) HYERS TM, TRICOMI SM, LIAO JJ. Inhibition of some human neutrophil functions by the cyclooxygenase inhibitor ketorolac tromethamine. *J Leukoc Biol* 1992; 51: 490-495.
- 2) DOMER F. Characterization of the analgesic activity of ketorolac in mice. *Eur J Pharmacol* 1990; 177: 127-135.
- 3) GILLIS JC, BROGDEN RN. KETOROLAC. A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. *Drugs* 1997; 53: 139-188.
- 4) CAMU F, VAN OVERBERGE L, BULLINGHAM R, LLOYD J. Hemodynamic effects of two intravenous doses of ketorolac tromethamine compared with morphine. *Pharmacotherapy* 1990; 10: 122S-126S.
- 5) BROWN CR, MOODIE JE, WILD VM, BYNUM LJ. Comparison of intravenous ketorolac tromethamine and morphine sulfate in the treatment of postoperative pain. *Pharmacotherapy* 1990; 10: 116S-121S.
- 6) LIU J, DING Y, WHITE PF, FEINSTEIN R, SHEAR JM. Effects of ketorolac on postoperative analgesia and ventilatory function after laparoscopic cholecystectomy. *Anesth Analg* 1993; 76:1061-1066.
- 7) PARKER RK, HOLTMANN B, SMITH I, WHITE PF. Use of ketorolac after lower abdominal surgery. *Anesthesiology* 1993; 78: 6-14.
- 8) READY LB, BROWN CR, STAHLGREN LH, EGAN KJ, ROSS B, WILD L, MOODIE JE, JONES SF, TOMMERAASEN M, TRIERWIELER M. Evaluation of intravenous ketorolac administered by bolus or infusion for treatment of postoperative pain. *Anesthesiology* 1994; 80: 1277-1286.
- 9) PARKER RK, HOLTMANN B, SMITH I, WHITE PF. Use of ketorolac after lower abdominal surgery *Anesthesiology* 1994; 80: 6-12.
- 10) VETTER TR, HEINER EJ. Intravenous ketorolac as an adjuvant to pediatric patient-controlled analgesia with morphine. *J Clin Anesth* 1994; 6: 110-113.
- 11) FORREST JB, HEITLINGER EL, REVELL S. Ketorolac for postoperative pain management in children. *Drug Saf* 1997; 16: 309-329.
- 12) CHAUHAN R-D, IDOM C-B, NOE H-N. Safety of ketorolac in the pediatric population after ureteroneocystostomy. *J Urol* 2001; 166: 1873-1875.
- 13) MILLER OF, BLOOM TL, SMITH LJ, McALEER IM, KAPLAN GW, KOLON TF. Early hospital discharge for intravesical ureteroneocystostomy. *J Urol* 2002; 167: 2556-2559.
- 14) PARK JM, HOUCK CS, SETHNA NF, SULLIVAN LJ, ATALA A, BORER JG, CILENTO BG, DIAMOND DA, PETERS CA, RETIK AB, BAUER SB. Ketorolac suppresses postoperative bladder spasms after pediatric ureteral reimplantation. *Anesth Analg* 2000; 91: 11-15.
- 15) DE OLIVEIRA JR GS, AGARWAL D, BENZON HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. *Anesth Analg* 2012; 114: 424-433.
- 16) RAMSAY MA, SAVEGE TM, SIMPSON BR, GOODWIN R. Controlled sedation with alphaxalone-alphadolone. *Br Med J* 1974; 2: 656-659.
- 17) VARRASSI G, MARINANGELI F, AGRÒ F, ALOE L, DE CILLIS P, DE NICOLA A, GIUNTA F, ISCHIA S, BALLABIO M, STEFANINI S. A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: analgesic efficacy and tolerability after gynecologic surgery. *Anesth Analg* 1999; 88: 611-616.
- 18) JO YY, HONG YJ, CHOI EK, KIL HK. Ketorolac or fentanyl continuous infusion for post-operative analgesia in children undergoing ureteroneocystostomy. *Acta Anesthesiol Scand* 2011; 55: 54-59.
- 19) ETCHES RC, WARRINER CB, BADNER N, BUCKLEY DN, BEATTIE WS, CHAN VWS, PARSON D, GIRARD M. Continuous intravenous administration of ketorolac reduces pain and morphine consumption after total hip or knee arthroplasty *Anesth Analg* 1995; 81: 1175-1180.
- 20) BURNS JW, AITKEN HA, BULLINGHAM RE, McARDLE CS, KENNY GN. Double-blind comparison of the morphine sparing effect of continuous and intermittent i.m. administration of ketorolac. *Br J Anaesth* 1991; 67: 235-238.
- 21) MROSZKSAK EJ, JUNG D, YEE J, BYNUM L, SEVELIUS H, MASSEY I. Ketorolac tromethamine pharmacokinetics and metabolism after intravenous, intramuscular, and oral administration in humans and animals. *Pharmacotherapy* 1990; 10: 33S-39S.
- 22) COHEN MN, CHRISTIANS U, HENTHORN T, TRAN Z-V, MOLL V, ZUK J, GALINKIN J. Pharmacokinetics of single-dose intravenous ketorolac in infants aged 2-11 months. *Anesth Analg* 2011; 112: 655-660.
- 23) DSIDA RM, WHEELER M, BIRMINGHAM PK, WANG Z, HEFFNER CL, COTÉ CJ, AVRAM MJ. Age-stratified pharmacokinetics of ketorolac tromethamine in pediatric surgical patients. *Anesth Analg* 2002; 94: 266-270.