Adding ketoprofen to intravenous patient-controlled analgesia with tramadol after major gynecological cancer surgery: A double-blinded, randomized, placebo-controlled clinical trial

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Summary

Ketoprofen is a NSAIDs of the 2-aryl propionic acid class commonly used in the treatment of inflammatory rheumatic disease, acute pain and fever. Clinically, ketoprofen seems to reduce morphine requirements by 33 to 40% with ketoprofen's supposed central mechanism of analgesia. We evaluated the efficacy and safety of intravenous (IV) ketoprofen as an adjuvant to IV PCA (patient controlled analgesia) with tramadol after major gynecological cancer surgery for postoperative analgesia.

Fifty patients were enrolled in this double-blinded, randomized, placebo-controlled study. Patients were allocated randomly to two groups: group I (25 patients) served as a control group, with patients receiving saline; group II (25 patients) received ketoprofen. Patients received an intravenous bolus of saline or 100 mg ketoprofen at the end of surgery. Then, PCA was given as a 20 mg tramadol bolus and 10 min lockout time. Pain relief was regularly assessed using a visual analog scale. Tramadol consumption, side-effects, and patient satisfaction were noted during the 24 hours after the surgery.

No significant difference was observed in pain score, side-effects and patient satisfaction between the groups ($p > 0.05$). The cumulative PCA-tramadol consumption was lower in the ketoprofen-treated patients than placebo-treated patients ($p < 0.05$).

Our results demonstrate that a single dose of 100 mg ketoprofen reduced tramadol consumption for treatment of postoperative pain after major gynecological cancer surgery.

Key words: Ketoprofen; Tramadol; Postoperative pain; PCA; Major gynecological surgery.

Introduction

In recent years there has been much progress in the understanding of the pathophysiology of acute pain and analgesic pharmacology. Nonsteroidal anti-inflamatory drugs (NSAIDs) have been regarded as the sole useful analgesic for mild to moderate pain because of their analgesic ceiling-effect depression [1]. However, the newer NSAIDs have been proposed as the sole analgesic for the treatment of moderate to severe pain [2]. Opioid analgesics are the cornerstone of postoperative pain management, especially after abdominal operations. They can however, produce nausea, vomiting, and respiratory depression [1].

Intravenous PCA with opioids is a popular method of delivering postoperative pain relief [3]. Tramadol is a weak, centrally-acting analgesic with a low affinity for μ opioid receptors, and it might provide efficacious postoperative pain relief with minimal sedative effects when used as intravenous PCA [4]. However, although it is minimally sedative and does not cause gastrointestinal stasis, its parenteral use appears to be associated with more nausea and vomiting than morphine or codeine [5]. Combining NSAIDs with opioid analgesics in the immediate postoperative period may improve analgesia and also opioid sparing, which results in improved respiratory function, a reduction in nausea and vomiting, and decreased sedation [6-8].

Ketoprofen is a NSAIDs of the 2-aryl propionic acid class commonly used in the treatment of inflammatory rheumatic disease, acute pain, and fever [9, 10]. Ketoprofen exerts its clinical effect by inhibition of prostaglandin synthesis, but also acts as a NMDA-receptor antagonist by means of the kynurenic acid. Clinically, ketoprofen seem to reduce morphine requirements by 33 to 40% with ketoprofen's supposed central mechanism of analgesia [10-12]. We are not aware of any reports about the effect of ketoprofen as an adjuvant to PCA with tramadol after major gynecological surgery.

The aim of the present double-blinded, randomized, placebo-controlled study was to evaluate the analgesic efficacy and safety of ketoprofen, in addition to IV PCA with tramadol after major gynecological cancer surgery for postoperative analgesia.

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Materials and Methods

Fifty female patients ASA I-II-III (American Society of Anesthesiologists physical status) scheduled to undergo major abdominal surgery with general anesthesia were enrolled in the study. Patients were operated on for gynecological cancer surgery, including cancer of the ovary, cervix and corpus uteri. Exclusion criteria were: age < 18 years, > 65; ASA IV, mentally incapable of using PCA; allergy to tramadol or ketoprofen; a history of peptic ulceration, gastrointestinal bleeding or any bleeding disorder; presence of severe renal (creatinine > 0.2 mg ml^{-1}), hepatic, cardiac or haemopoietic disease; a history of chronic pain, routine analgesic use, and use of NSAID, opioids, diuretics or angiotensin converting enzyme inhibitors in the 24 h preceding surgery.

During the preoperative assessment, all patients were instructed on the use of a PCA pump (Abbott Pain Manager, Abbott Laboratories, Chicago, IL) and a 10 cm visual analogue scale [(VAS) 0 = no pain, 10 = worst pain imaginable]. Premedication consisted of 10 mg of oral diazepam one hour before transfer to the operating room. Anaesthesia was induced with fentanyl 1.5 μg kg^{-1} followed by thiopental 4-5 mg kg^{-1}. Tracheal intubation was facilitated by atracurium 0.5 mg kg^{-1} and lung ventilation was controlled. Anaesthesia was maintained with isoflurane (1 to 1.5%) in a mixture of 50% nitrous oxide in oxygen and supplemented with intermittent bolus atracurium and fentanyl. At the end of surgery the residual neuromuscular block was antagonized with neostigmine (0.04 mg kg^{-1}) + atropine (0.02 mg kg^{-1}). Intraoperative data included type of surgery, duration of surgery and total opioid dose.

Patients were allocated randomly to two groups: group I served as a control group, with patients receiving placebo (saline); group II received ketoprofen. Patients received an intravenous bolus of 100 mg of saline or ketoprofen at the end of surgery. The PCA system was programmed to deliver 20 mg of tramadol in a 1 ml solution on demand. The lockout interval was set to ten min. When analgesia was required in the recovery room 1 mg kg^{-1} of tramadol as an intravenous loading dose was administered to all patients. The patients were given 10-20 mg IV tramadol administrated in bolus doses at 10-min intervals until they appeared to be comfortable and were capable of using an Abbott PCA device. Thereafter, patients activated the PCA pumps themselves. All patients were evaluated for 24 h after the surgery.

The same doctor of the Pain Management Team who did not know about the patient grouping made all postoperative assessments. All assessments were made at 6-h intervals for pain at rest only. Assessment of the PCA tramadol consumption was noted at the end of the study. Patients were asked "How effective was your medication at relieving your pain?" This five-point verbal raiting scale (1 = excellent, 5 = very poor) has been shown to have discriminatory power. The following adverse effects were noted over the 24h period: respiratory depression defined as a respiratory rate below 10/min, confusion or disorientation, nausea and vomiting, gastralgia, broncospasm and cutaneous rash or other allergic events. Nausea and vomiting were assessed on a four-point scale: (0: no nausea, 1 = nausea, 2 = retching, 3 = single vomiting, 4 = multiple vomiting) [13]. If two score points or more were reached (i.e. vomiting or retching occurred) or if patients specially demanded antiemetics or reported intolerable nausea, 10 mg of metoclopramide was given intravenously as a rescue antiemetic.

Statistical analysis was done with the Statistical Package for Social Sciences (SPSS), version 10.1. Data are presented as mean ± SD and numbers. The results were statistically compared by the Mann-Whitney U and the Student's t-tests. A p value < 0.05 was considered statistically significant.

Results

There were no significant differences between the groups regarding age, body weight, duration of surgery and dose of fentanyl received in the operating room ($p > 0.05$) (Table 1).

There were no significant differences regarding pain scores between the groups ($p > 0.05$) (Table 2). The cumulative PCA-tramadol consumption was lower in the ketoprofen treated patients than the placebo-treated patients ($p < 0.05$) (Table 2).

Side-effects observed during the study and patient satisfaction are summarized in Table 3. There were no significant differences in the incidence of nausea-vomiting and rescue antiemetic treatment ($p > 0.05$). The control of analgesia was good in most patients. No discernible adverse effects accompanying ketoprofen usage were observed.

Table 1. — *Patient characteristics and operative data.*

	Group I (placebo) (n = 25)	Group II (ketoprofen) (n = 25)
Age (yrs.)	54.6 ± 11.7	50.7 ± 12 6
Weight (kg)	73.5 ± 8.8	69.5 ± 10.1
ASA physical status		
I	5	8
II	14	12
III	6	5
Type of surgery		
cancer of the ovary	9	11
cancer of the cervix	10	10
cancer of the corpus uteri	6	4
Intraoperative fentanyl dose (mg)	430.5 ± 46.8	480.2 ± 39.5
Duration of surgery (mins.)	152.7 ± 45.2	164.5 ± 37.8

Table 2. — *Pain scores (VAS: 0-10) and tramadol consumption.*

	Group I (placebo) (n = 25)	Group II (ketoprofen) (n = 25)
Pain score		
6 h	3.1 ± 0.6	2.9 ± 0.9
12 h	2.8 ± 0.7	2.3 ± 0.8
18 h	1.9 ± 0.7	1.6 ± 0.5
24 h	1.5 ± 0.6	1.1 ± 0.4
Tramadol consumption (mg/24 h)	484.4 ± 86.7	332.6 ± 65.3*

Values are mean ± SD; VAS: visual analogue scale; *p < 0.05.

Table 3. — *Side-effects and patient satisfaction.*

	Group I (placebo) (n = 25)	Group II (ketoprofen) (n = 25)
Side-effects		
Nausea	11	10
Mild	1	–
Moderate	3	5
Severe	7	5
Retching	3	2
Vomiting	7	5
Antiemetic rescue	18	14
Patients satisfaction		
Excellent	1	1
Good	15	18
Moderate	8	6
Poor	1	–
Very poor	–	–

Values are number of patients.

Discussion

In this study we demonstrated that the effect on pain relief and side-effects are comparable between PCA with tramadol and PCA with tramadol + ketoprofen after major gynecological cancer surgery. The results of this study demonstrated that single dose ketoprofen reduced the tramadol consumption. Postoperative pain after major abdominal surgery is known to be intensive. $NSAID_S$ have generally proved reliable as supplementary analgesics in relieving postoperative pain after major abdominal surgery. Peripheral tissue injury produces inflammatory pain which results from an increased sensitivity of high-threshold nociceptor neurons at their peripheral terminals when they are exposed to the inflammatory mediators and other chemicals released in reaction to tissue damage [14]. Preventing this peripheral sensitization has been assumed to be the major action of $NSAID_S$ by inhibition of prostaglandin production by the enzyme cyclooxygenase [7]. Thus if peripheral sensitization is decreased, central sensitization would be decreased, and postoperative pain would be reduced. Ketoprofen, a nonsteroidal antiinflamatory drug structurally similar to ibuprofen, has analgesic, antiinflamatory, and antipyretic properties [15]. Because its onset of action is 55-60 min and its plasma half-life is short (1.8 ± 0.4 h), ketoprofen is considered to be safer than other $NSAID_S$ in the postoperative period [10]. Likar *et al.* [11] suggested that ketoprofen is an effective postoperative analgesic in combination with an opioid, but has no preemptive effect. Therefore, patients received 100 mg of ketoprofen intravenously at the end of surgery in this study. Cepeda *et al.* [1] suggested that $NSAID_S$ should be used as an adjuvant, but not as the sole analgesic, for the management of moderate to severe postoperative pain [1]. In this study, ketoprofen was used as an adjuvant analgesic.

Our results demonstrate that single dose ketoprofen reduced tramadol consumption. A similar benefit has been previously demonstrated by combining $NSAID_S$ with opioids, where the addition of these analgesics reduced the consumption of opioids [6, 8, 16]. Rorarius *et al.* [12] observed that ketoprofen reduces opioid requirements by 40% after caesarean section. Aubrun *et al.* [10] reported that ketoprofen reduced morphine requirements and improved postoperative analgesia in patients undergoing major spinal surgery. Ketoprofen has a synergistic effect with opioids, improving the degree and quality of analgesia and reducing the incidence of adverse effects [17].

$NSAID_S$ decrease platelet aggregation and increase bleeding time and thus may increase perioperative and postoperative bleeding [18]. However, a study using ketoprofen has not detected problems with surgical bleeding, bleeding time, blood transfusion requirements, or postoperative bleeding [10]. In this study we did not observe bleeding in any patient. Gastrointestinal complications (gastritis, ulcer perforation and bleeding) have been well described with the chronic use of $NSAID_S$ [10]. However, these complications have also been described after only one week of treatment [19]. No discernible adverse effects accompanying ketoprofen usage were observed during our study. Postoperative nausea and vomiting (PONV) is one of the most common and annoying adverse effects after anesthesia. A number of factors, including age, obesity, previous history of experience nausea and vomiting, surgical procedure, anaesthetic technique, intra-/postoperative use of opioids, and postoperative pain, influence likelihood and extent of PONV [20]. In this study, all patients underwent major gynecological surgery with a standardized anaesthetic regimen. There were no significant differences between the groups with regard to age, body weight, duration of surgery, duration of anaesthesia, or dose of fentanyl received in the operating room. However, patients undergoing major gynecological surgery are at increased risk of nausea and vomiting [21]. Also, the administration of opioids with a PCA system can aggravate PONV [22]. Kokki *et al.* [15] reported that continuous IV ketoprofen improved postoperative pain and reduced epidural sufentanil requirements. However, the incidence of opioid-related adverse effects did not change. In the present study, although nausea and vomiting were observed more frequently in the placebo group, these differences were not statistically significant. Although, tramadol is a weak, centrally-acting analgesic with a low affinity for μ opioid receptors, the most feared complication of opioids is respiratory depression. In this study, we did not observe a low respiratory rate or sedation in any patient.

In conclusion, our study demonstrates the usefulness of ketoprofen as an adjuvant to PCA tramadol for treatment of postoperative pain after major gynecological cancer surgery, with good control of analgesia and less tramadol consumption.

References

[1] Cepeda M. S., Vargas L., Ortegon G., Sanchez M., Carr D. B.: "Comparative analgesic efficacy of patient-controlled analgesia with ketoralac versus". *Anesth. Analg.,* 1995, *80,* 1150.

[2] Brown C., Mazzulla J., Mok M. *et al.*: "Comparison of repeat doses of intramuscular ketoralac tromethamine and morphine sulfate for analgesia after major surgery". *Pharmacotherapy,* 1990, *10,* 45.

[3] Reeves M., Lindholm D. E., Myles P. S., Fletcher H., Hunt J. O.: "Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: A double-blinded, randomized controlled trial". *Anesth. Analg.,* 2001, *93,* 116.

[4] Silvasti M., Svartling N., Pitkanen M. *et al.:* "Comparison of intravenous patient-controlled analgesia with tramadol vs morphine after microvascular breasth reconstruction". *Eur. J. Anaesth.,* 2000, *17,* 448.

[5] Crighton I. M., Martin P. H., Hobbs G. J. *et al.*: "A comparison of the effects of intravenous tramadol, codeine, and morphine on gastric emptying in human volunteers". *Anesth. Analg.,* 1998, *87,* 445.

[6] Palazon J. H., Tortosa J. A., Martinez-Lage J. F., Perez-Flores D.: "Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery". *Anesth. Analg.*, 2001, *92,* 1473.

[7] Dahl J. B., Kehlet H.: "Non-steroidal anti-inflamatory drugs: rationale for use in severe postoperative pain". *Br. J. Anaesth.,* 1991, *66,* 703.

[8] Ethches R. C., Warriner C. B., Badner N. *et al.*: "Continuous intravenous administration of ketorolac reduces pain and morphine consumption after total hip or knee arthoplasty". *Anesth. Analg.*, 1995, *81*, 1175.
[9] Kokki H., Tuomilehto H., Karvinen M.: "Pharmacokinetics of ketoprofen following oral and intramuscular administration in young children". *Eur. J. Clin. Pharmacol.*, 2001, *57*, 643.
[10] Aubrun F., Langeron O., Heitz D., Copriat P., Riou B.: "Randomized, placebo-controlled study of the postoperative analgesic effects of ketoprofen after spinal fusion surgery". *Acta Anaesthesiol. Scand.*, 2000, *44*, 934.
[11] Likar R., Krumpholz R., Mathiaschitz K., Pipam W., Burtscher M., Ozegovic G., Breschan C., Bernatzy G., Sittl R.: "The preemptive action of ketoprofen. Randomized, double-blinded study with gynecological operations". *Anaesthesist.*, 1997, *46*, 186.
[12] Rorarius M. G., Suominen P., Baer G. A., Romppanen O., Tuimala R.: "Diclofenac and ketoprofen for pain treatment after elective caesarean section". *Br. J. Anaesth.*, 1993, *70*, 293.
[13] Piper S. N., Triem J. G., Maleck W. *et al.*: "Placebo-controlled comparison of dolasetron and metoklopramide in preventing postoperative nausea and vomiting in patients undergoing hysterectomy". *Eur. J. Anaesth.*, 2001, *18*, 251.
[14] Woolf C. J., Chong M.-S.: "Preemptive analgesia - treating postoperative pain by preventing the establishment of central sensitization". *Anesth. Analg.*, 1993, *77*, 362.
[15] Koki A., Tuovinen K., Hendolin H.: "The effect of intravenous ketoprofen on postoperative epidural sufentanil analgesia in children". *Anesth. Analg.*, 1999, *88*, 1036.
[16] Parker R. K., Holtmann B., Smith I., Whie P. F.: "Use ketorolac after lower abdominal surgery". *Anesthesiology*, 1994, *80*, 6.
[17] Nicanne E., Kokki H., Tuovinen K.: "IV perioperative ketoprofen in small children during adenoidectomy". *Br. J. Anaesth.*, 1997, *78*, 24.
[18] Conrad K. A., Fagan T. C., Mackie M. J., Mayshar P. V.: "Effects of ketoralac tromethamine on hemostasis in volunters". *Clin. Pharmacol. Ther.*, 1988, *43*, 542.
[19] Soll A. H., Weinstein W. M., Kurata J., McCarty D.: "Nonsteroidal anti-inflamatory drugs and peptic ulcer disease". *Ann. Intern. Med.*, 1991, *114*, 307.
[20] Watcha M. F., White P.F.: "Postoperative nausea and vomiting:its etiology, treatment and prevention". *Anesthesiology*, 1992, *77*, 162.
[21] Madej T. H., Simpson K. H.: "Comparison of the use of domperidone, droperidol and metoclopramide in the prevention of nausea and vomiting following major gynecology surgery". *Br. J. Anaesth.*, 1986, *58*, 884.
[22] Robinson S. L., Fell D.: "Nausea and vomiting with use of a patient-controlled analgesia system". *Anaesthesia*, 1991, *46*, 580.

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