The preemptive use of diclofenac sodium in combination with ketamine and remifentanil does not enhance postoperative analgesia after laparoscopic gynecological procedures

Ozgur Canbay, MD, Ozlem Karakas, MD, Nalan Celebi, MD, Lutfiye Peker, MD, Fehmi Coskun, MD, Ulku Aypar, MD.

ABSTRACT

Objective: To evaluate the preemptive effects of diclofenac sodium, in combination with remifentanil and ketamine.

Methods: A prospective, randomized, double blind, placebo-controlled trial was carried out at the Hacettepe University Hospital, Ankara, Turkey from September to December 2004. Forty-three, American Society of Anesthesiology physical status group I-II women, aged >18 years, who would undergo both diagnostic and operative laparoscopic surgery were randomly assigned into 2 groups. All patients received intraoperative 0.1 μgr.kg^{-1}min^{-1} remifentanil infusion. Diclofenac (1 mg.kg^{-1} intramuscular) was administered, 20 minutes before the operation. Ketamine (0.8 mg.kg^{-1} intravenously) was administered 5 minutes before the skin incision and at completion of skin closure. We divided the patients into 2 groups; Group I (diclofenac + remifentanil + ketamine), Group II (remifentanil + ketamine). Pain was evaluated postoperatively using the visual analogue scale (VAS) while global satisfaction by verbal rating scale (VRS).

Results: All 43 female patients have a mean ± SD age of 32.3 ± 6.5 years, height of 163 ± 5.3 cm, and weight of 62.9 ± 9.5 kg. The VAS and VRS scores and also time to first analgesic request were not different between the groups. In all groups, >98% of the patients were satisfied or very satisfied.

Conclusion: We have not found any preemptive or additive effect of diclofenac sodium with the concomitant use of ketamine.

Saudi Med J 2006; Vol. 27 (5): 642-645

It is rational that for effective relief of postoperative pain and for preemptive analgesia to be effective, an intraoperative blockade of pain must be maintained and then followed by active management of pain in the postoperative period.[1] This has recently been defined that preventive analgesia could be provided simply before incision. In addition to the timing of analgesia, multimodal analgesia is a reasonable and effective approach to pain management.[2]

The aim of multimodal analgesia combinations is to reduce postoperative pain. Analgesia offered by the multimodal approach would be additive and possibly synergistic.[1] Many beneficial effects of non-steroidal anti-inflammatory drugs (NSAIDs) are produced by inhibiting COX-2 enzymes and these drugs reduce inflammation and pain.[1] The NSAIDs are used commonly to reduce postoperative pain and narcotic requirements, and so as the narcotic side

From the Department of Anesthesia, Hacettepe University Faculty of Medicine, Ankara, *Turkey.*

Received 31st October 2005. Accepted for publication in final form 28th February 2006.

Address correspondence and reprint request to: Dr. Ozgur Canbay, Department of Anesthesiology, Hacettepe University Faculty of Medicine, Sihhiye 06100, Ankara, *Turkey.* Tel. +90 (312) 3051207. Fax. +90 (312) 3109600. E-mail: ozgurcanbay@yahoo.com

effects. Preoperative administration of diclofenac has shown to relieve postoperative pain and to reduce postoperative analgesic requirements.[3] Some studies have demonstrated a preemptive analgesic effect of diclofenac[3,4] while some others have not.[5-8]

It has been reported that μ-opioid receptor activation results in a sustained increase in glutamate synaptic effectiveness at the N-methyl-D-aspartate (NMDA) receptor level, a system associated with central hypersensitivity to pain[9] and also central sensitization in inflammatory pain states when reinforced by an opioid treatment, which could be prevented by NMDA receptors blockade.[10] The use of ketamine as a preemptive analgesic has been encouraging as ketamine improves postoperative pain control and can reduce the opioid-related adverse side effects at the same time.[1]

We aimed to evaluate the preemptive effects of diclofenac sodium, in combination with remifentanil and ketamine.

Methods. Forty-three adult women, American Association of Anesthesiology (ASA) physical status group I-II, undergoing elective gynecological laparoscopy procedures were enrolled in this randomized, prospective, double-blinded protocol approved by the ethical committee. The study was carried out at Hacettepe University Hospital, Ankara, Turkey from September to December 2004. After obtaining written, informed consent, patients were assigned to one of the 2 treatment groups according to a computer-generated list of random numbers. The exclusion criteria included patients requiring chronic analgesic medication, having psychological disorders, and having a history of drug or alcohol abuse and also peptic ulcus complaints.

Patients were not pre medicated and they were instructed on the use of a 10 cm long visual analogue rating scale (VAS) with 0 cm identifying no pain and 10 cm the worst imaginable pain. Global satisfaction was scored by the patients 24 and 48 hours after the operation on a 5 point verbal rating scale (0 = very dissatisfied, 1 = dissatisfied, 2 = neutral, 3 = satisfied, 4 = very satisfied.)

All patients received 0.1 μgr.kg^{-1}min^{-1} remifentanil infusion before the start and the end of the surgery. Diclofenac [1 mg.kg^{-1} intramuscular (i.m.)] was administered, 20 minutes before the operation. Ketamine [0.8 mg/kg^{-1} intravenously (i.v.)] was administered 5 minutes before the skin incision and at completion of skin closure. Group I receive diclofenac + remifentanil + ketamine while group 2 receives remifentanil + ketamine.

General anesthesia was induced with propofol (2 mg.kg^{-1} i.v.). Tracheal intubation was facilitated with vecuronium bromide (0.1 mg.kg^{-1} i.v.). Anesthesia was maintained with desflurane and nitrous oxide 66% in oxygen. The inspired concentration of desflurane was adjusted to maintain an adequate depth of anesthesia. Meperidine 1 mg.kg^{-1} was administered for rescue medication. All patients were given 2.5 mg of neostigmine and 0.5 mg of atropin to reverse the residual muscle paralysis. Naproxen sodium (550 mg) was prescribed for all patients to take postoperatively at home when needed. The time and the number of pills that the patients had taken in the first 24 and 48 hours were learned through phone calls.

In the recovery room, intensity of pain, requirement for meperidine "rescue" medication, and postoperative side effects (example; nausea, vomiting, secretions, confusion, agitation and psychomimetic reactions) were recorded 0, 15, 30, 60, 90, 120 minutes intervals and also evaluated at 24, 48 hours postoperatively and also blood samples were collected to determine the basal and intraoperative cortisol levels.

We calculated that this study had a power of 80% to detect differences between groups, which would be significant at the 5% level. This calculation was similar to that used in several other studies investigating the presence or absence of preemptive analgesia in clinically relevant circumstances.[11-13] Statistical analysis was performed using the one way analysis of variance and chi-square tests where appropriate. The *p* value of 0.05 or less was considered as statistically significant

Results. Demographic data, anesthesia and surgery duration, and intraoperative cortisol levels were comparable, basal cortisol levels were high in group I which was not clinically important and type of surgery was not different among groups (**Table 1**).

The VAS scores were similar between groups (**Figure 1**). Pain intensity was maximal at the 15 minutes evaluation in all groups (group I: 4.26 ± 3.03, group II: 5.55 ± 2.67). Time to first analgesic request and the recovery periods did not differ between groups. Naproxen sodium consumption 24 and 48 hours after the operation was similar.

The incidence of side effects was comparable in all groups. In all groups, >98% of the patients were satisfied or very satisfied.

Discussion. Given the expanding role of ambulatory surgery and the need to facilitate an earlier hospital discharge, improving postoperative pain control has become an increasingly important issue for all anesthesiologists. Multimodal or balanced analgesic techniques involving the use of smaller doses of opioids in combination with non-opioid analgesic

Table 1 - Demographic characteristics, anesthesia and surgery duration, basal and intraoperative cortisol levels for the 2 treatment groups (mean ± SD).

Variants	Group I	Group II
Number	23	20
Age (year)	33.6 ± 6	30.6 ± 6.8
Weight (kg)	64.1 ± 9.2	61.6 ± 9.9
Height (cm)	163.5 ± 4.6	162.5 ± 6
Surgery time (minutes)	35.3 ± 23.6	45.8 ± 35.1
Anesthesia time (minutes)	44.5 ± 22.2	57.9 ± 32.7
Basal cortisol levels (ug/dL)	15.3 ± 6	11.6 ± 3.6
Intraoperative cortisol levels (ug/dL)	15 ± 6.2	13.2 ± 5.2

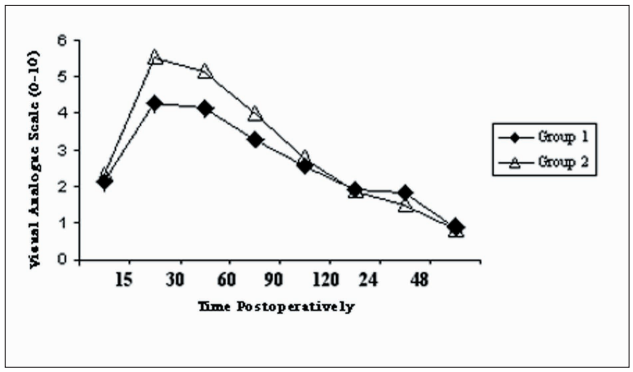

Figure 1 - Pain scores after surgery by using a visual analogue rating scale (0 = no pain to 10 = most severe pain) *p* = NS.

drugs such as NSAIDs and ketamine, to minimize the variety of perioperative side effects of opioids, are becoming increasingly popular approaches to preventing pain after surgery. However, in our study we have not found any preemptive or additive effect of diclofenac sodium with the concomitant use of ketamine.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as adjuncts to opioids to provide analgesia following major surgery. Synergistic or additive analgesia may result from a combination of drugs acting by different mechanisms. This improves analgesia with less opioid use and also reduces possible side effects. However, repeated administration of NSAIDs may impair renal function, particularly in an elderly surgical population. Hence, it may be preferable to administer a single dose of NSAID as a supplement to postoperative analgesia.[14]

In the last decade, there has been a renewed interest in the use of sub anesthetic doses of ketamine for the treatment of acute and chronic pain. In the late 1990's, multiple prospective, randomized, controlled study has shown the efficacy of low dose of ketamine for postoperative pain relief, for analgesia during regional and local anesthesia, and for opioid sparing effect.[17] Some of the recent clinical data demonstrated that a single small dose of ketamine given during various outpatients' surgeries improved pain scores and reduced postoperative analgesic consumption by 35-40%.[18,19] Elhakim et al[20] found that administration of a single small dose of ketamine before tonsillectomy enhanced postoperative analgesia, reduced post-operative analgesic requirement, and improved swallowing and quality of oral intake during the first postoperative day. In that study, all children received rectal diclofenac 2 $mg.kg^{-1}$ and fentanyl 1 $mg.kg^{-1}$ i.v. before surgery. In our study, although we have used a larger dose of ketamine (0.8 $mg.kg^{-1}$ i.v., preoperatively and at the end of surgery) we could not find similar results for the postoperative analgesic requirements.

Recently, excitatory neurotransmitters (acting through N-methyl-D-aspartate (NMDA) receptor) have been incriminated in the development and maintenance of pathologic pain states after tissue injuries (mainly hyperalgesia and allodynia).[21] Schmid et al[22] were concluded that sub anesthetic doses of ketamine in association with opiates, or local anesthetics or other anesthetics significantly improve pain scores, reduce the requirements for rescue medication, and the area of hyperalgesia surrounding the surgical wound. But according to these authors, more information was needed to concern the best dose, the preferential route of administration and the long-term effect on residual pain. Recently De Kock et al[23] concluded in their study that a sub anesthetic dose of ketamine (0.5 $mg.kg^{-1}$ bolus followed by an infusion of 0.25 $mg.kg^{-1}$ hr^{-1}) was a useful adjuvant for the perioperative balanced analgesia and the preferential route of administration was the systemic route. We have not used an infusion dose of ketamine and not measured the hyperalgesia surrounding the surgical wound that can explain the counter results of our study with the aforementioned results. The results of our study support the conclusion of Annetta et al[24] mentioning that, at present, non-definitive conclusion can be drawn; more data are needed to define the possible long term effects and clinical goal of ketamine use.[24]

When the inflammatory process is induced, the sensation of pain is increased. NSAIDs perfectly block this inflammatory process. NMDA receptors

have also been demonstrated to contribute the inflammatory processes in laboratory studies.[25,26] Diclofenac possesses a clear central nervous system (CNS) action reversible by naloxone, greater anti-inflammatory potency, a metabolite with anti-inflammatory action.[27]

This shared anti-inflammatory and central mechanism directed us to administer the diclofenac sodium with ketamine to evaluate the quality of the postoperative analgesia they may offer. No clinically important side effects which could impede us to use ketamine in these doses were observed.

In general, multimodal analgesia can improve postoperative pain management in ambulatory surgery. It is particularly important to improve postoperative pain following gynecological laparoscopic surgery. To obtain the optimum combination for the intra and postoperative pain management for gynecological ambulatory surgery, further clinical studies evaluating the balanced anesthesia with preemptive use of NSAIDs concomitantly with bolus and infusion doses of ketamine should be studied clinically.

References

1. Redmond M, Florence B, Glass PSA. Effective analgesic modalities for ambulatory patients. ***Anesthesiol Clin North America*** 2003; 21: 329-346 .
2. Jin F, Chung F. Multimodal analgesia for postoperative pain control. ***J Clin Anesth*** 2001; 13: 524-539.
3. Wuolijoki E, Oikarinen VJ, Ylipaavalniemi P, Hampf G, Tolvanen M. Effective postoperative pain control by preoperative injection of diclofenac. ***Eur J Clin Pharm*** 1987; 32: 249-252.
4. Parke TJ, Lowson SM, Uncles DR, Daughtery MO, Sitzman BT. Pre-emptive versus post-surgical administration of ketorolac for hysterectomy. ***Eur J Anaesth*** 1995; 12: 549-553.
5. Deal SE, Pandak WM, Heuman DM. Lack of efficacy of ketorolac tromethamine for analgesia on patients undergoing colonoscopy. ***Am J Gastroenterol*** 1993; 88: 1050-1053.
6. Higgins MS, Givogre JL, Marco AP, Blumenthal PD, Furman WR. Recovery from outpatient laparoscopic tubal ligation is not improved by preoperative administration of ketorolac or ibuprofen. ***Anesth Analg*** 1994; 79: 274-280.
7. Chui PT, Gin T. A comparison between ketorolac and diclofenac in laparoscopic sterilization. ***Eur J Anaesth*** 1995; 12: 597-601.
8. Zacharias M, Hunter KM, Baker AB. Effectiveness of preoperative analgesics on postoperative dental pain: a study. ***Anesth Prog*** 1996; 43: 92-96.
9. Kissin I, Cheryl BA, Edwin BL. The effect of ketamine on opioid-induced acute tolerance: Can it explain reduction of opioid consumption with ketamine-opioid analgesic consumptions? ***Anesth Analg*** 2000; 91:1483-1488.
10. Rivat C, Laulin J-P, Corcuff J-B, Celerier E, Pain L, Simonnet G Fentanyl Enhancement of Carrageenan-induced Long-lasting Hyperalgesia in Rats: Prevention by the N-methyl-d-aspartate Receptor Antagonist Ketamine. ***Anesthesiology*** 2002; 96: 381-391.
11. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, et al. Preemptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. ***Anesthesiology*** 1996; 77: 439-446.
12. Tordoff SG, Brossy M, Rowbothom DJ, James JN, James R, Raphael JH. The effect of pre-incisional infiltration with lignocaine on postoperative pain after molar teeth extraction under general anesthesia. ***Anaesthesia*** 1996; 51: 585-587.
13. Dahl JB, Hansen BL, Hjortso NC, Erichsen CJ, Moiniche S, Kehlet H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. ***Br J Anaesth*** 1992; 69: 4-8.
14. Alexander R, El-Moalem HE, Gan TJ. Comparison of the morphine-sparing effects of diclofenac sodium and ketorolac tromethamine after major orthopedic surgery. ***J Clin Anesth*** 2002; 14: 187-192.
15. Anderson SK, Al Shaikh BA. Diclofenac in combination with opiate infusion after joint replacement surgery. ***Anesth Intensive Care*** 1991; 19:535-538.
16. Tigersted I, Janhunen L, Tammisto T. Efficacy of diclofenac in a single prophylactic dose in postoperative pain. ***Ann Clin Res*** 1987; 19: 18-22.
17. White PF. The Changing Role of Non-Opioid Analgesic Techniques in the Management of Postoperative Pain. ***Anesth Analg*** 2005; 101: S5-S22.
18. Menigaux C, Fletcher D, Dupont X, Guignard B, Guirimand F, Chauvin M. The benefits of intraoperative small-dose Ketamine on postoperative pain after anterior cruciate ligament repair. ***Anesth Analg*** 2000; 90: 129-135.
19. Suzuki M, Tsueda K, Lansing PS, Tolan MM, Fuhrman TM, lgnacio CI, et al. Small-dose Ketamine enhances morphine induced analgesia after outpatient's surgery. ***Anesth Analg*** 1999; 89: 98-103.
20. Elhakim M, Khalafallah Z, El-Fattah HA, Farouk S, Khattab A. Ketamine reduces swallowing-evoked pain after pediatric tonsillectomy. ***Acta Anaesthesiol Scand*** 2003; 47: 604-609.
21. Wilcox GL. Excitatory neurotransmitters and pain. In: Bond MR, Charlton JE, Woolf CJ, editors. Proceedings of the VIth World Congress of Pain, Pain research and clinical management, 4. Amsterdam: Elsevier; 1991. p. 97-118.
22. Schmid RL, Sandler AN, Katz J. Use and efficacy of low dose ketamine in management of acute postoperative pain: a review of current techniques and outcomes. ***Pain*** 1999; 82: 11-125.
23. De Kock M, Lavand'homme P, Waterloos H. Balanced analgesia in the perioperative period: is there a place for ketamine? ***Pain*** 2001; 92: 373-380.
24. Annetta MG, Iemma D, Garisto C, Tafani C, Proietti R. Ketamine: New Indications for an Old Drug. ***Current Drug Targets*** 2005; 6: 789-794.
25. Kawasaki T, Ogata M, Kawasaki C. Ketamine suppresses proinflammatory cytokine production in human whole blood in vitro. ***Anaesth Analg*** 1999; 89: 665-669.
26. Schaible HG, Grubb BD, Neugebauer V, Oppmann M. The effects of NMDA antagonists on neuronal activity in cat spinal cord evoked by acute inflammation in the knee joint. ***Eur J Neurosci*** 1991; 3: 981-991.
27. Silvanto M, Lappi M, Rosenberg PH. Comparison of the opioid-sparing efficacy of diclofenac and ketoprofen for 3 days after knee arthroplasty. ***Acta Anaesthesiol Scand*** 2002; 46: 322-328.