The Effect of Preoperative Ketorolac on WBC Response and Pain in Laparoscopic Surgery for Endometriosis

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Surgical stress causes changes in the composition of white blood cells (WBCs). Ketorolac is believed to have analgesic effects and to reduce the stress response and may therefore improve postoperative outcomes. The aim of this study was to assess the effect of preoperative ketorolac on the WBC subsets in patients who had laparoscopic surgery for endometriosis. Fifty patients who had laparoscopic surgery for endometriosis were randomly assigned to one of two groups: the ketorolac group (n = 25) received ketorolac 0.5 mg/kg before the induction of anesthesia, and the control group (n = 25) received saline. White cell count, differential, and pathology studies were done immediately after surgery, on postoperative day 1, and on postoperative day 3. We compared the baseline values within and between the two groups. We also assessed postoperative pain and side effects. The time that elapsed before the first patient request for analgesia, total meperidine dose and VAS (Visual Analog Scale) for postoperative pain were significantly lower in the ketorolac group than in the control group. Compared to the pre- surgical values, there was an increase in total WBC count and percentage of neutrophils, but a decrease in percentages of lymphocytes, monocytes, eosinophils, basophils, and leucocytes. Total WBC count, neutrophils, monocytes, eosinophils and leucocytes showed significant differences between the two groups. The incidences of postoperative side effects, such as nausea, dizziness, headache, and shoulder pain were not different between the groups. Preoperative ketorolac reduced postoperative pain and influenced the WBC response in laparoscopic surgery for endometriosis.

Key Words: Pain, postoperative, ketorolac, laparoscopic, immune response, white blood cell.

INTRODUCTION

Endometriosis lesions can be removed during laparoscopy by surgical excision with scissor and bipolar coagulation. This can cause broad intra-peritoneal thermal damage. Some evidence shows that the release of the excitatory amino-acid, nitric oxide, and prostaglandin E_2 (PGE_2) play a critical role in the development of peripheral tactile and thermal hypersensitivity in models of pain due to inflammation.[1,2] Major surgery or trauma is followed by changes in the composition of white blood cells (WBCs). These changes are characterized as lymphopenia and polymorphonuclear leucocytosis.[3,4] The stress response that is initiated in major surgeries causes a release of cortisol and also affects leukocyte numbers.[5]

The synthesis of PGE_2 can be controlled by a cyclooxygenase (COX) inhibitor such as ketorolac tromethamine.[6] Ketorolac is an injectable nonsteroidal anti-inflammatory drug (NSAID) that is thought to have analgesic effects and to reduce the stress response and may therefore improve postoperative outcomes.[7]

We tested the hypothesis that the administration of ketorolac before skin incision reduces postoperative pain and improves blood cell responses in women undergoing laparoscopic surgery for endometriosis.

MATERIALS AND METHODS

This was a randomized, placebo-controlled, double-blind study. After Institutional Review Board approval, written informed consent was obtained from a total of 50 patients scheduled for

elective laparoscopic surgery for endometriosis grade III or IV.[8] We excluded patients with allergies to NSAIDs or opioids, an active ulcer within 6 months, a history of bleeding problems, recent anticoagulant use, and patients currently pregnant, breast-feeding, or receiving steroids. We also excluded patients with ASA physical status of III or greater, and patients with significant coexisting hepatic, renal, neurological, pulmonary, or cardiac disease.

Patients were randomly assigned to one of two groups. Randomization was carried out by means of a computerized random-numbers table. The ketorolac group (n = 25) received IV ketorolac 0.5 mg/kg, and the placebo group (n = 25) received saline of the same volume. The medications were prepared by a nurse who was not involved in the procedure. The surgeon, anesthesiologist and the patient were all blinded to the identity of the medication used.

No premedication was given. General anesthesia consisted of propofol (2 mg/kg), fentanyl (0.05 mg), rocuronium (0.5 mg/kg) for induction, and rocuronium and enflurane in nitrous oxide-oxygen for maintenance.

Venous blood samples were collected four times throughout the study period (30 minutes before induction as a baseline, immediately after surgery, 1 day postoperatively, and 3 days postoperatively). The changes of white cell count and the compositions immediately after surgery, on postoperative day 1 and on postoperative day 3 were compared to the baseline values within the groups and these values were compared between the groups. Hematological measurements were performed using an ADVIA® 120 (Bayer Co. Dublin, Ireland).

Postoperative pain was assessed using a 100 mm visual analog scale (VAS, 0 = no pain; 100 = worst pain possible) at 2, 6, 12, and 24 hours after surgery. Total analgesic doses during 72 hours were recorded. The time elapsed between the end of surgery and the first analgesic request (first analgesic time) was also recorded. Postoperative side effects and treatments were observed. An independent observer who was blinded to the study protocol collected the data in the recovery room.

Power analysis was performed using an α-value of 0.05 and a power of 0.9 to determine the sample size sufficient for establishing a significant difference in peripheral blood response based on the results of the preliminary study. A sample consisting of at least 24 patients per group was necessary.

Demographic and clinical data of the two groups were compared using the Student's t-test. Because neither the peripheral blood cell count nor the analgesic dose was distributed normally, the Mann-Whitney test was used to compare the two groups during the same time period. Within the groups, comparisons of the peripheral blood cell levels to the baseline values were performed using the repeated measures ANOVA on ranks and the Dunnet method. Chi-square and Fisher's exact tests examined group differences for adverse side effects. A p value less than 0.05 was considered to be significant.

RESULTS

Between the two groups, no significant differences in age, weight, height, or clinical data, such as duration of anesthesia, blood loss, and amount of total fluid administered were found (Table 1).

The total meperidine dose (mg) required to control postoperative pain was 128.5 ± 91.2 in the control group and 74.5 ± 42.1 in the ketorolac group (p< 0.05). Significantly more patients in the control group (17/25, 68%) required postoperative analgesics compared to the ketorolac group (7/25, 28%). The first analgesic request time was 69.4 ± 11.9 (min) in the control group and 226.3 ± 36.3 (min) in the ketorolac group (p< 0.05). The VAS values for pain at 2, 6, and 12 hours after surgery were significantly lower in the ketorolac group than in the control group (Fig. 1).

Total white cell count including neutrophils and monocytes showed significant differences between the two groups at 3 days after surgery. Eosinophil percentages were significantly higher in the ketorolac group compared to the control group at day 1 and day 3 after surgery (Table 2). Both groups showed a significant drop in postoperative red blood cell, hemoglobin, and hematocrit levels compared with baseline values (Table 3). There are no significant red blood cell pattern

Jeong-Yeon Hong

Table 1. Demographic and Clinical Data

	Control group (n = 25)	Ketorolac group (n = 25)
Age (yrs)	33.2 ± 6.6	32.9 ± 5.2
Weight (kg)	56.7 ± 7.7	54.3 ± 4.5
Height (cm)	161.2 ± 5.2	160.8 ± 4.1
Duration of anesthesia (min)	90.6 ± 20.4	83.5 ± 23.8
Total fluid (mL)	923 ± 122	1038 ± 185
Estimated blood loss (mL)	221 ± 46	205 ± 55
Urine output (mL)	155 ± 70	145 ± 55

Data are mean ± SD.
There are no significant differences between the two groups.

Table 2. Changes in White Blood Cell Responses

Parameters	Baseline	Postop. (Immediate)	Postop. (1 day)	Postop. (3 days)
WBC (10^3/μL)				
Control group (n=25)	6.3 ± 2.3	8.0 ± 2.5[†]	8.4 ± 2.8[†]	6.1 ± 1.5
Ketorolac group (n=25)	5.9 ± 1.8	7.0 ± 2.1[†]	8.2 ± 1.9[†]	5.2 ± 1.2*
Neutrophils (%)				
Control group	60.0 ± 18.4	60.2 ± 14.1	76.1 ± 8.2[†]	56.9 ± 7.8
Ketorolac group	55.1 ± 12.3	59.7 ± 15.2	73.1 ± 6.9[†]	50.0 ± 8.3*
Lymphocytes (%)				
Control group	34.3 ± 7.2	32.8 ± 12.3	20.6 ± 6.8[†]	33.0 ± 7.3
Ketorolac group	33.6 ± 9.3	32.5 ± 13.5	18.8 ± 5.1[†]	35.3 ± 7.4
Monocytes (%)				
Control group	4. ± 1.3	3.5 ± 1.3[†]	4.9 ± 1.5	4.7 ± 1.1
Ketorolac group	4.7 ± 1.3	3.6 ± 1.2[†]	5.0 ± 1.4	5.5 ± 1.6*
Eosinophils (%)				
Control group	2.0 ± 1.3	1.0 ± 0.8[†]	0.8 ± 0.6[†]	3.0 ± 1.6[†]
Ketorolac group	2.6 ± 1.8	1.6 ± 1.3[†]	1.6 ± 1.0*[†]	4.3 ± 1.1*[†]
Basophils (%)				
Control group	0.8 ± 0.5	0.6 ± 0.3	0.4 ± 0.1[†]	0.6 ± 0.2
Ketorolac group	0.7 ± 0.3	0.6 ± 0.2	0.4 ± 0.2[†]	0.7 ± 0.2

Data are mean ± SD.
Total white cell count, neutrophil, and monocyte showed significant differences between the two groups at 3 days after surgery. Percentages of Eosinophils were significantly higher in the ketorolac group compared to the control group at day 1 and day 3 after surgery.
*p< 0.05 compared to the control group.
[†]p< 0.05 compared to the baseline values.

Table 3. Changes in Red Blood Cell, Hemoglobin, and Hematocrit Levels

Parameters	Baseline	Postop. (Immediate)	Postop. (1 day)	Postop. (3 days)
RBC (10^6/μL)				
Control group	4.3 ± 0.3	3.9 ± 0.4*	3.7 ± 0.3*	3.8 ± 0.5*
Ketorolac group	4.3 ± 0.3	3.9 ± 0.3*	3.7 ± 0.3*	3.8 ± 0.4*
Hg (g/dL)				
Control group	12.3 ± 0.9	11.4 ± 0.8*	10.9 ± 0.9*	10.9 ± 1.2*
Ketorolac group	12.4 ± 1.0	11.5 ± 0.8*	10.9 ± 0.8*	11.0 ± 0.8*
Hct (%)				
Control group	37.0 ± 2.1	33.8 ± 2.2*	32.2 ± 2.5*	32.5 ± 3.8*
Ketorolac group	37.0 ± 2.4	34.1 ± 2.2*	32.4 ± 2.6*	33.1 ± 2.7*

Data are mean ± SD.
Postoperative red blood cell, hemoglobin, and hematocrit levels decreased significantly compared with baseline values in the two groups. There are no significant differences between the two groups.
*$p < 0.05$ compared to the baseline values.

differences between the two groups.

The incidences of postoperative side effects, such as nausea, dizziness, headache, and shoulder pain were essentially the same for both groups. There were no serious side effects such as oozing or bleeding which are occasionally observed as a postoperative complication of ketorolac use.

DISCUSSION

Preemptive analgesia is currently being used for the management of postoperative pain and is no longer actively researched. However, the clinical efficacy of NSAIDs is controversial. Norman et al. reported that intravenous ketorolac appears to have preemptive analgesic effects in patients undergoing ankle fracture repair.[9] However, a study by Cabell did not demonstrate preemptive analgesic effects in laparoscopic gynecologic surgery.[10] Preemptive analgesic effects are difficult to show in human experiments because of the differences in surgical procedures, dose, route, and timing of administration. Our study supports the finding that the preoperative use of 30 mg of ketorolac for endometriosis surgery that causes broad thermal tissue damage provides not only opioid-sparing, but also preemptive analgesic effects. Evidence regarding the preemptive an-

algesic effects of ketorolac requires controlled studies comparing effects before and after surgery. However, our report did not follow such a design. In our study, postoperative pain scores were lessened even beyond the 12-hour duration of ketorolac which suggested preemptive effects. Our findings are consistent with previous studies in which preoperative administration of an NSAID decreased postoperative opioid requirements following laparoscopic surgery.[11-13]

One concern with the use of ketorolac has been the possibility of NSAID-specific adverse side effects such as oozing or oliguria. FDA guidelines for intravenous ketorolac use suggest using a dose of 30 mg to minimize these effects. In our study, no adverse events related to the use of ketorolac 30 mg were observed. There were no significant differences between the two groups in the occurrence of postoperative side effects.

In addition to pain management, ketorolac is thought to help maintain immune homeostasis. Leukocytes are the major cellular components of the inflammatory and immune responses which also include neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Major surgical stress causes lymphopenia with leucocytosis.[3,4] The increased release of cortisol that accompanies the stress response or the exogenous administration of adrenaline as is done in major surgeries, can also

affect leukocyte numbers.[5] In the two groups of our study, there was a significant increase in white cell and neutrophil counts, but a decrease in lymphocytes, monocytes, eosinophils, and basophils compared to the baseline. The ketorolac group, however, showed more effective recovery in these variables in the postoperative period than the control group. Changes in circulating leukocyte numbers may be caused by an absolute change in total leukocyte count or an alteration in the fraction of leukocytes. An increase in the number of blood neutrophils is called neutrophilia. The granules of neutrophils are readily released extracellularly, and their mobilization is believed to be important in modulating inflammation. In both groups of our study, neutrophil counts increased 24 hours after surgery and later returned to baseline values. However, at 3 days after surgery, the percentage of neutrophils was significantly lower in the ketorolac group than in the control group.

Monocytes are important secretory cells that, through their receptors and secretory products, participate in many complex immunologic and inflammatory processes not attributed to neutrophils. Eosinophils and neutrophils share similar morphology, lysosomal constituents, chemotactic responses, phagocytic capacity, and oxidative metabolism. Eosinophenia occurs during a stress response, such as acute infection, or the administration of corticosteroids.[14] The mechanism of eosinopenia is unknown and there is no known adverse clinical effect of eosinopenia. In our results, it was observed that the percentages of monocytes and eosinophils decreased significantly following surgery. In the ketorolac group, monocytes increased at 3 days after surgery and eosinophils were found to be increased at days 1 and 3 after surgery. These levels were significantly higher than the control group.

Lymphocyte is a primary mediator in humoral and cellular immune responses. The lymphocyte levels did not show significant differences between the two groups, although there were decreases in lymphocytes at postoperative day 1 compared to the baselines in the both groups. In the late postoperative period, there were significant decreases of lymphocyte and neutrophil levels in our study. Further studies are required

to explain these findings. The variations of WBC responses may be due to the differences in surgical procedures, subjects, or study designs.[15-17]

Our results confirmed that ketorolac can positively influence leukocyte distribution after surgery, although the clinical efficacy is unclear. Several factors are likely to be involved in mediating the white cell responses to surgery. Physiologic cortisol and catecholamines can influence the distribution of leukocytes.[18,19] Unfortunately, we did not monitor hormone levels such as cortisol, prolactin, or catecholamines, or neutrophil function, subtypes of lymphocytes and leukocytes, CRP, interleukin-6, or plasma ketorolac concentration. These may be considered limitations of this study. The above laboratory findings are more reliable than peripheral WBC responses, but are more complicated, time consuming, and clinically limited.

In summary, this study demonstrated greater improvement in postoperative pain scores and reduced requirements for meperidine following the administration of preoperative ketorolac compared to the control. Postoperative leukocytosis, neutrophilia, and a decrease in monocytes and eosinophils after surgery were affected by preoperative intravenous ketorolac.

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