Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy

Total abdominal histerektomide preemptif intravenöz parasetamolün analjezik etkisi

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Summary

Objectives: Paracetamol is primarily thought to be a cyclooxygenase inhibitor acting through the central nervous system. Indirect effects of paracetamol are through the serotoninergic system as a non-opioid analgesic. In this study, total abdominal hysterectomy patients were given intravenous (iv) paracetamol 1 g preoperatively or intraoperatively to assess its postoperative analgesic effects.

Methods: 90 patients undergoing total abdominal hysterectomy were enrolled into the study. Patients were randomized into three groups: in Group I, iv paracetamol 1 g was given 30 minutes prior to induction. In Group II, iv paracetamol 1 g was given prior to skin closure. Group III served as the control group and received saline as placebo. Postoperatively, all patients received morphine via patient-controlled analgesia pump. Postoperatively, rest and activity pain scores, sedation scores, hemodynamic parameters, postoperative morphine consumption, side effects, patient satisfaction, and total hospital stay were recorded.

Results: In the control group, at rest and movement pain scores and total morphine consumption via patient-controlled analgesia were higher than in Groups I and II. When Groups I and II were compared, total morphine consumption was much greater in Group II. Intravenous paracetamol intraoperatively and postoperatively did not result in any hemodynamic effects.

Conclusion: In total abdominal hysterectomy, preemptive iv paracetamol 1 g provided good quality postoperative analgesia, with decreased consumption of morphine and minimal side effects.

Key words: Laparotomy; morphine; paracetamol; postoperative analgesia.

Özet

Amaç: *Parasetamol, primer olarak santral sinir sistemi üzerinde santral siklooksijenaz inhibisyonu yoluyla ve olasılıkla serotoninerjik sistemle indirekt etki ettiğine inanılan nonopioid bir ajandır. Bu çalışmada, laparatomi ile total abdominal histerektomi yapılan olgulara intravenöz (iv) 1 gr parasetamol, preoperatif veya intraoperatif verilerek ameliyat sonrası analjezik etkisinin saptanması amaçlandı.*

Gereç ve Yöntem: *Elektif total abdominal histerektomi yapılacak 90 olgu randomize edilerek eşit üç gruba ayrıldı. Grup I'deki olgulara indüksiyondan 30 dakika önce 1 gr iv parasetamol, Grup II'deki olgulara cilt insizyonu kapatılmadan önce 1 gr iv parasetamol, Grup III'deki olgulara indüksiyondan 30 dakika önce ve cilt insizyonu kapatılmadan önce 100 ml iv serum fizyolojik verildi. Ameliyat sonrası tüm olgulara morfin ile iv hasta kontrollü analjezi uygulandı. Ameliyat sonrası dönemde olguların dinlenme ve hareket halindeki ağrı skorları, sedasyon skorları, hemodinamik parametreler, morfin tüketimi, yan etkiler, hasta ve hemşire tedavi memnuniyeti, hastanede kalış süreleri izlenerek kaydedildi.*

Bulgular: *Kontrol grubunda hareket ve dinlenme halindeki ağrı skorları ve ameliyat sonrası tüm zaman dilimlerindeki morfin tüketimi ile kümülatif morfin tüketimi Grup I ve Grup II'den anlamlı olarak yüksek bulundu. Grup I ile Grup II karşılaştırıldığında Grup II'de toplam morfin tüketimi anlamlı olarak yüksek bulundu. Hiçbir olguda parasetamolün intraoperatif ve postoperatif hemodinami üzerine olumsuz etkileri saptanmadı.*

Sonuç: *Total abdominal histerektomi operasyonu olan olgularda uygulanan preemptif 1 gr iv parasetamolün ameliyat sonrası dönemde etkin bir analjezi sağladığı, ameliyat sonrası morfin tüketimini ve yan etkileri azaltarak, hasta memnuniyetini arttırdığı saptandı.*

Anahtar sözcükler: Laparatomi; morfin; parasetamol; ameliyat sonrası analjezi.

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As knowledge of the epidemiology and pathophysiology of postoperative pain increases, a new analgesic concept has been developed and applied for the prevention of pain whereby analgesic treatment is started prior to trauma and surgical intervention. Within this concept, referred to as preemptive analgesia, it is believed that through application of an analgesic medicine or technique, pain will either subside or be prevented prior to the painful stimulus. This affect is achieved by suppressing, either together or separately, central or peripheral sensitization. Preemptive analgesia gives rise to a subsiding pain pattern, a decrease in analgesic requirements, and a decline in morbidity, promoting wellness and shortening the length of hospital stays.[1,2]

Local anesthetics, opioids, non-steroid anti-inflammatory drugs (NSAIDs) and acetaminophen group drugs can be delivered either alone or in combination for preemptive analgesia.[3] Paracetamol is a non-opioid agent, and it is believed that it primarily acts upon the central nervous system by way of central cyclooxygenase inhibition, and probably has an indirect influence on the serotoninergic system. Paracetamol has a good safety profile and easily passes through the brain barrier, which assures it as an effective analgesic.[4]

In the present study, our aim was to assess postoperative morphine consumption, sedation and pain scores, side effects, patient satisfaction, and length of hospital stay in total abdominal hysterectomy patients with laparotomy, who received intravenous (iv) paracetamol 1 g either preoperatively or intraoperatively, and to compare results with control patients who received placebo.

Materials and Methods

Ethics council approval was obtained from Uludağ University and the Faculty of Medicine, along with a written informed consent from the patients. A total of 90 patients undergoing an elective total abdominal hysterectomy by laparotomy in an operating room and under general anesthesia were included into the prospective, randomized, planned study. Patients were allocated into three groups.

The criteria for exclusion from the study were:

1. American Society of Anesthesiologists (ASA) scores III and IV,
2. History of allergic reactions to paracetamol or morphine,
3. History of usage of paracetamol, opioids, or NSAIDs in the 48 hours (h) before requiring chronic analgesic treatment,
4. Chronic alcoholism, deficiency of liver and kidney,
5. Cardiovascular system illness,
6. Bleeding diathesis,
7. Cases in such a mental or cultural condition that they are unable to use the patient-controlled analgesia (PCA) device.

By visiting the patients one day before the operation, related information and training was given about the anesthesia method to be applied, usage of the PCA device and the Visual Analog Scale (VAS). Pharmacological premedication was not applied to patients in whom oral intake was cut off 8 h prior to the operation.

The 90 patients matching the working criteria were divided into three equal groups by randomization:

In Group I (n=30, preemptive group), iv paracetamol 1 g (100 ml) was administered 30 minutes (min) prior to induction, and 100 ml iv normal saline was administered prior to closing of the skin incision.

In Group II (n=30, intraoperative group), 100 ml iv normal saline was given 30 min before induction and iv paracetamol 1 g (100 ml) was administered prior to closing the skin incision.

In Group III (n=30, control group), 100 ml iv normal saline was given 30 min before induction and prior to closing of the skin incision.

Patients' age, weight, height, ASA classification and operation period were recorded. The patients were pre-oxygenized for 3 min with 100% oxygen. For induction, 1 mg/kg 2% lidocaine, 2-2.5 mg/kg propofol, 2 μg/kg fentanyl citrate, and 0.6 mg/kg rocuronium were given. Following intubation, maintenance of general anesthesia was accomplished by providing 2% sevoflurane in 40/60 oxygen/nitrous oxide and, if required, 0.1 mg/kg rocuronium. End-

tidal carbon dioxide ($ETCO_2$) monitoring was also done. No additional analgesics were dispensed over the entire course of the operation.

Intraoperatively, mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO_2) and $ETCO_2$ values were recorded at 10, 20, 30, 40, 60, 90 and 120 min.

At the end of the operation, the patients were transferred to the recovery room. Before leaving the operating room, however, iv PCA with morphine was given postoperatively to all patients (1 mg/ml morphine and a PCA device programmed for a 2 mg bolus with a 10-min lockout period and a 0.4 mg/kg 4-h limit). A 2 mg loading dosage was given at the end of the operation.

For postoperative pain assessment, VAS was used (VAS: 0-10; 0: no pain, 10: worst pain imaginable). The sedation levels of the patients were defined in accordance with the Ramsay Sedation Scale (RSS).[5]

The VAS scores of the patients at postoperative 15 and 30 min, and at 1, 2, 4, 8, 12, and 24 h, during at rest (VAS_R) and movement (VAS_M), were recorded by measurement of RSS, MAP, and SpO_2. The total morphine consumption during the same periods and over 24 h was recorded in mg.

Side effects, such as nausea, vomiting, respiration depression, itching, allergic reaction, stomach irritation, diarrhea, and constipation, were cross-examined and recorded. Since a postoperative 24 h urine cannula was fitted, there was no urine retardation follow-up.

Furthermore, the patients were asked whether or not they would desire the same pain management applied in this case to be applied in the future, and their responses were recorded. The length of hospital stay of the cases was tracked, and their discharge terms from the hospital were recorded as well.

The authors estimated that there was a 0.85 probability (in SD) that a patient who received paracetamol would report lower pain intensity on VAS scoring and lower PCA morphine consumption than a patient who received saline solution. Assuming that the pain scores would be compared using the Wilcoxon's rank sum test with two-sided 10% level of statistical significance and 90% power, the authors calculated that at least 81 patients (27 per group) were required.

The Biostatistical Department of Uludağ University Faculty of Medicine performed the statistical analysis. For the statistical analysis of the data, Kruskall-Wallis, chi-squared and Mann-Whitney U tests were utilized. A p-value <0.05 was accepted as statistically significant.

Results

Ninety patients were involved in the study. Two patients in Group I and 3 patients each in Groups II and III were excluded from the study. When the demographic data and operation values of the 82 patients included in the study were compared, no statistically significant differences were determined between groups (Table 1).

No statistically significant differences were found between groups with respect to MAP, HR, SpO_2 and $ETCO_2$ values at the beginning of the operation or intraoperatively.

Table 1. Demographic data

	Group I (n=28)	Group II (n=27)	Group III (n=27)
Age (year)	50.37±6.56	47.73±7.20	49.90±6.40
Height (cm)	161.43±4.88	161.17±4.87	162.07±4.77
Weight (kg)	69.67±10.68	72.67±13.00	68.10±14.36
ASA I / II	21 / 9	19 / 11	21 / 9
Operation time (min)	121.60±29.43	114.30±21.80	118.83±22.58

Data are given as mean ± SD or case number (n); ASA: American Society of Anesthesiologists.

Table 2. Postoperative PCA morphine consumption

	Group I (n=28)	Group II (n=27)	Group III (n=27)
0-1 hr	4.67±1.10	5.07±1.11	8.60±1.19*†
1-2 hr	4.53±1.57	4.13±1.04	10.20±1.71*†
2-4 hr	4.60±1.40	4.67±1.49	12.27±1.94*†
4-8 hr	4.07±1.33	7.20±2.00*	11.15±1.95*†
8-12 hr	4.00±1.39	8.40±1.69*	10.00±2.92*†
12-24 hr	3.47±1.04	6.07±1.53*	10.60±2.25*†
Total morphine consumption (mg)	25.93±5.69	35.73±5.24*	62.93±8.67*†

Data are given as mean ± SD; PCA: Patient-controlled analgesia;
* p<0.05; compared to Group I; † p<0.05; compared to Group II.

When the VAS_R scores of the patients in Group III were compared with Groups I and II, they were found to be significantly higher at all time points (p<0.05). The VAS_M values of the cases in Group III were also found to be significantly higher (p<0.05) than the values of Groups I and II (Figures 1 and 2).

When the sedation scores of the groups were compared, there was no statistical difference between groups.

The morphine consumption of the cases is shown in Table 2. The morphine consumption in Group III at all postoperative time frames was found to be significantly higher (p<0.05) than that in Groups I and II. The morphine consumption levels of cases in Groups II and III at 4-8 h, 8-12 h, and 12-24 h time intervals were significantly higher than in Group I (p<0.05). When the total morphine consumption amounts for 24 h were compared, those of the control group were significantly higher than of groups that received medication (p<0.05). In addition, when medication groups were compared, the total morphine consumption of Group II was found to be significantly higher (p<0.05).

The incidence of side effects such as postoperative nausea, vomiting, itching and respiratory depression is shown in Table 3 according to patient groups. When the treatment-dependent side effect incidences were compared, nausea, vomiting, and itching were found to be significantly higher in the control group (p<0.05). No respiratory depression requiring naloxone usage occurred in any patient.

Seventy-one patients (86.5%) preferred the postoperative pain management for a future application, whereas 11 (13.4%) did not; 2 of these were in Group II and the other 9 in Group III.

When the lengths of hospital stay were compared,

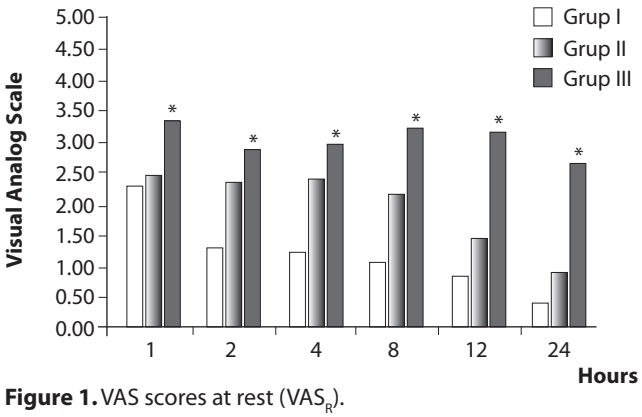

Figure 1. VAS scores at rest (VAS_R).
* p<0.05; compared to Groups I & II.

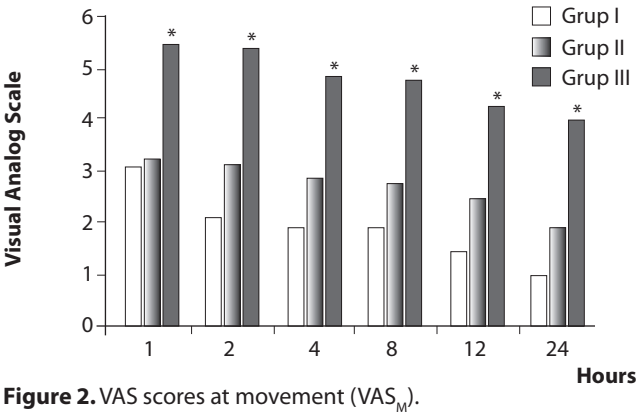

Figure 2. VAS scores at movement (VAS_M).
* p<0.05; compared to Groups I & II.

Table 3. Side effects and hospital stay

	Group I (n=28)	Group II (n=27)	Group III (n=27)
Nausea	3 (10.7%)	3 (11.1%)	9 (33.3%) *
Vomiting	2 (6.7%)	3 (10.0%)	9 (27.6%) *
Itching	0 (0%)	1 (3.3%)	6 (22.2%) *
SpO_2 < 95%	0 (0%)	0 (0.0%)	0 (0.0%)
Hospital stay (day)	5.03±0.76	5.20±0.92	6.43±1.38 *

Data are given as mean ± SD or case number (n) (%);
* p<0.05; compared to Groups I & II.

it was determined that the hospital stay for cases in Group III was extended with respect to the other groups (p<0.05) (Table 3).

Discussion

In the present study, we used iv paracetamol 1 g, use of which as a preemptive analgesic in hysterectomy cases has recently begun. We assessed its effects on intraoperative hemodynamics, postoperative analgesia effectiveness, morphine consumption, frequency of side effects, and hospital stay length, and determined that administration of paracetamol 1 g 30 min before induction resulted in decreased postoperative resting and in-motion VAS values and total morphine consumption over 24 h. Furthermore, we observed fewer side effects and a shorter length of hospital stay.

The negative effects caused by postoperative pain can be diminished with good postoperative analgesia. The requirement of treatment of postoperative pain is accepted by all authorities. Insufficient postoperative pain control leads to complications in both the short- and long-term periods. Among these complications, atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism, psychological trauma, elongated intestinal distension, urine retardation, myocardial ischemia, and infarction may be considered.[6]

Due to the negative effects and complications it causes in the patient, postoperative pain has to be treated in a fast and effective manner. Pain management should be started prior to pain initiation. With a good analgesic treatment plan for the patient in place, the anxiety, morbidity, cost, and length of hospital stay in the postoperative period are decreased. Therefore, postoperative analgesia management is important. As of yet, no optimal medicine or method for postoperative pain management has been found that is devoid of side effects.[7] The aim of preemptive analgesia, which has been investigated in recent years, is to provide analgesia prior to a painful stimulus to prevent central sensitization caused by the painful stimulus and, consequently, to decrease the need for postoperative analgesia.[8]

The methods and agents for which preemptive analgesic effectiveness has been researched are mostly NSAIDs, opioids, ketamine, peripheral local anesthetics and epidural analgesia.[3]

It was demonstrated that paracetamol rapidly passes the blood-brain barrier, reaches a high concentration in the cerebrospinal fluid and has an anti-nociceptive effect mediated by the central nervous system.[9,10] This central effect has been regarded primarily as an indirect and reciprocal influence through cyclooxygenase enzyme inhibition, and probably through the serotoninergic system as well. Besides this central effect, it is accepted that paracetamol has a peripheral anti-inflammatory influence, although this effect is somewhat limited.[11]

It was demonstrated that iv paracetamol has a faster analgesic effect at early time points, a higher effectiveness and a longer analgesic effect than an equivalent paracetamol dosage compared to oral application.[12] Clinical studies have found that 1 g iv paracetamol employed alone is just as effective as 30 mg ketorolac, 75 mg diclofenac or 10 mg morphine.[13,14] Studies have also shown that iv paracetamol has an opioid-sparing effect and enhances patient satisfac-

tion by reducing the opioid requirement.[15-17]

In one study,[18] the authors preoperatively dispensed either oral oxycodone in one group (n=10) or 1,000 mg oral paracetamol in another group (n=10) of female cholecystectomy patients and evaluated postoperative pain and side effects in each group; they found similar postoperative pain scores and side effects, with no difference determined between the groups.

In another study[19] on 60 patients who had a panretinal photocoagulation operation, they administered 1,000 mg oral paracetamol as a preemptive analgesic and compared the results with a placebo group. Subsequently, they found that postoperative pain scores subsided in the preemptive group in 24 h. In the study by Hein[20] of 60 patients who had undergone a minor gynecological operation, they dispensed 8 mg oral lornoxicam to one group 60 min before the induction and 1,000 mg oral paracetamol to another group and compared both groups to a control group. It was found that the VAS pain scores at postoperative 30 and 60 min were lower in the groups in which medicine was administered than in the control group, with similar scores observed in the lornoxicam and paracetamol groups. In our study, similarly, VAS scores were lower in the paracetamol group in the postoperative period.

Varrasi and colleagues[21] assessed the relative morphine consumption in a combined analgesic regimen after gynecologic surgery with iv doses of propacetamol 2 g or ketorolac 30 mg. Patients were assessed regarding total dose of morphine, pain intensity and global efficacy. They established that total morphine requirements were not significantly different between the propacetamol (10.6±4.8 mg) and ketorolac (10.2±4.4 mg) groups. The evolution of pain intensity also showed similar patterns in the two groups.

The VAS scores at rest and in motion were determined. In our study, the VAS pain scores were found to be <3 in Groups I and II at the postoperative 1st h at rest and in motion, but in Group III it was observed that those scores were >3 while in motion. These results indicate that sufficient analgesic effectiveness was ensured after the postoperative 1st h in Groups I and II. We believe that the high VAS pain scores of Group III while in motion points out the difficulty of applying effective analgesia with postoperative iv morphine after laparotomies. Additionally, the low values of the pain scores in the groups under medication may be explained by decreases in excitability in the central nervous system through blockade of nociceptive stimuli before damaging tissue architecture.

In our study, the total morphine consumptions for all time frames and at 24 h in the preemptive Group I and intraoperative Group II were lower than in Group III. The total morphine consumptions of the patients in Group II at the 4-8, 8-12, and 12-24 h time intervals and at 24 h were found to be significantly higher than in Group I.

Reuben,[22] in their study comprising 60 patients who underwent arthroscopic knee surgery under spinal anesthesia, employed 50 mg rofecoxib as a preoperative analgesic and administered it before incision and at the end of the operation. They found that when compared with the placebo group, the first analgesia demand time was longer and total 24 h morphine consumption and pain scores were lower in the preemptive group relative to the other two groups.

In another study of 73 patients undergoing breast biopsy, it was determined that parenteral administration of 20 mg tenoxicam both preemptively and postoperatively increased the first analgesia demand time and lowered the VAS scores in the preemptive group. Consequently, it was deduced that tenoxicam has preemptive analgesic effectiveness in breast surgery.[23]

Dahl and colleagues[24] evaluated the postoperative opioid-sparing effect of a pre-operative oral ibuprofen 800 mg and paracetamol 1000 mg in elective open hysterectomy patients that received test drugs orally 1 h before the start of anesthesia. They found differences between the groups in postoperative pain measured by any variable or opioid consumption at any time and stated that orally given ibuprofen or paracetamol does not have a postoperative analgesic or opioid-sparing effect. This may have been due to first-pass elimination of orally medicated drugs.

In our study, total morphine consumption at all time frames and for 24 h in the preemptive Groups I and II was lower as compared to Group III. Total morphine consumptions of the patients in Group II at 4-8, 8-12, and 12-24 h time intervals and at 24 h were significantly higher as compared to Group I. The greater analgesic requirement observed in Group II as compared to Group I can be explained by the gradual reduction in effect of the paracetamol administered postoperatively after 4-6 h. We believe that since the preemptively delivered paracetamol prevents central sensitization, its analgesic effect continues longer than its effect period. As in many studies carried out with iv paracetamol usage,[13,17,20] our study did not encounter any negative effects in hemodynamic parameters, such as intraoperative and postoperative SpO_2, HR, and MAP.

Depending on the dosage of opioids delivered by the PCA, complications such as respiration depression, sedation, nausea, vomiting, urine retention, and itch may develop. Sedation is the earliest indicator of respiratory depression. The RSS for sedation is generally used to assess this.[25] In the present study, we did not find an increase in sedation scale values to result in the occurrence of respiratory depression. Although the decreases seen in postoperative SpO_2 in the control group were statistically significant, they were negligible from a clinical point of view. Notwithstanding, the incidences of nausea, vomiting and itching were more frequent in Group III due to more morphine consumption.

The success of postoperative pain management has an influence on patient satisfaction. There are many factors that define this success. Patient anxiety, communication with service nurses, and preoperative enlightenment are a few of these factors. In our study, we asked the patients if they were satisfied with the present postoperative pain management at 24 h and whether or not they would desire the same pain management to be applied in the future. We determined from the responses given that the gratification rate was high in all groups. The majority of the patients emphasized that would like the same pain management to be applied in the future as well. Eleven patients did not want the same pain management in the future and 9 of them belonged to the control group. This finding suggests that patients who received paracetamol were more satisfied than those with iv PCA alone.

The length of hospital stay was significantly shorter in Groups I and II as compared to Group III. Lesser cumulative morphine dosage and side effect incidence should ensure a shortened length of hospital stay.

In conclusion, our findings indicate that preemptively administered iv paracetamol 1 g in patients undergoing a total abdominal hysterectomy operation has no negative effects on intraoperative or postoperative hemodynamic parameters, ensures an effective analgesia during the postoperative period, increases patient satisfaction by reducing postoperative morphine consumption and side effects, and thereby shortens the length of hospital stay. Therefore, we believe preemptively administered iv paracetamol 1 g can be confidently given for postoperative analgesia after abdominal hysterectomy.

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