KLİNİK ÇALIŞMA / CLINICAL RESEARCH

TOTAL ABDOMİNAL HİSTEREKTOMİ SONRASI EPİDURAL HASTA KONTROLLÜ ANALJEZİ İLE MULTİMODAL ANALJEZİNİN ETKİNLİK VE YAN ETKİLERİNİN KARŞILAŞTIRILMASI

THE OPTIMAL POSTOPERATIVE ANALGESIA METHOD AFTER TOTAL ABDOMINAL HYSTERECTOMY: EPIDURAL PATIENT-CONTROLLED ANALGESIA OR MULTIMODAL ANALGESIA

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ÖZET

Amaç: *Çalışmamızın amacı; total abdominal histerektomi geçirecek hastalarda epidural hasta kontrollü analjezi (HKA) yöntemi ile multimodal analjezinin etkinliklerinin karşılaştırılmasıdır.*

Yöntem: *Total abdominal histerektomi operasyonu geçirecek 20-60 yaş arası, ASA I-II grubu 60 hasta rastgele epidural analjezi grubu (Grup E) ve multimodal analjezi grubu (Grup M) olarak 30 hasta içeren iki gruba ayrıldı. Grup E'de hastalara yan yatar pozisyonda, L3-4 intervertebral aralıktan epidural aralığa girilerek 15 ml %0.25 bupivakain HCl ve 100 µg fentanil epidural kateterden uygulandı. Tüm hastalarda anestezi indüksiyonu 2 mg kg^{-1} propofol ve 0.5 mg kg^{-1} atraküryum intravenöz (iv) ile sağlandı. Endotrakeal entübasyon sonrasında anestezi idamesi 2 MAK sevofluran ve O_2 içinde %70 N_2O ile kontrollü ventilasyonla sürdürüldü. Peroperatif kalp atım hızı, ortalama arter basıncı, periferik oksijen satürasyonu ve tidal sonu karbondioksit değerleri 5'er dakikalık aralar ile kaydedildi. Grup E'de peroperatif dönemde % 0.25 bupivakain ve 3 µg ml^{-1} fentanil içeren solüsyondan 10 ml sa^{-1} infüzyon uygulandı. Derlenmede ise %0.125 bupivakain + 3 µg ml^{-1} fentanil içeren solüsyon ile bazal infüzyon 5 ml sa^{-1}, bolus 4 ml, kilitli kalma süresi 15 dk olacak şekilde hasta kontrollü epidural analjezi (HKEA) başlandı. Grup M'ye indüksiyonda lornoksikam 16 mg + deksametazon 8 mg + parasetamol 1gram (g) iv uygulandı. Operasyon bitiminde cerrahi insizyon hattına cerrah tarafından %0.25 bupivakain 20 ml ile infiltrasyon yapıldı. Derlenmede 10 mg ml^{-1} meperidin içeren solüsyon ile bolus 1.5 ml, kilitli kalma süresi 8 dk olacak şekilde iv HKA başlandı. Aynı zamanda parasetamol 3x1 g ve lornoksikam 2x16 mg iv uygulanmak üzere postoperatif analjezi planlandı. Hastalarda postoperatif 48 saat boyunca; ortalama arter basıncı, kalp atım sayısı, VAS skorları, uygulanan ek analjezik miktarları ve yan etkiler, GİS fonksiyonları (ilk bağırsak sesi zamanı, ilk defekasyon zamanı), ilk mobilizasyon zamanı ve taburculuk zamanı kaydedildi.*

Bulgular: *İki grup arasında ortalama arter basıncı, kalp atım sayısı, VAS skorları, uygulanan ek analjezik miktarları ve yan etkiler, ilk bağırsak sesi duyulma zamanı, ilk mobilizasyon zamanı ve taburculuk zamanı açısından anlamlı farklılık saptanmadı ($p>0.05$). Epidural analjezi grubunda ilk defekasyon zamanının belirgin şekilde erken olduğu saptandı ($p<0.05$).*

Sonuç: *Total abdominal histerektomi geçiren hastalarda epidural analjezi yöntemi ile ilk defekasyon zamanı daha erken olmasına karşın, eşdeğer analjezi sağlayabilmesi nedeni ile multimodal analjezinin (iv meperidin HKA, lornoksikam, parasetamol, deksametazon ve yarayeri infiltrasyonu) iyi bir alternatif olabileceği kanısına varıldı.*

ANAHTAR KELİMELER: *Postoperatif analjezi; multimodal analjezi; hasta kontrollü analjezi; total abdominal histerektomi*

SUMMARY

Objective*: The aim of our study was to compare the efficacy and side effects of patient-controlled epidural analgesia (PCEA) and multimodal analgesia after total abdominal hysterectomy (TAH).*

Method: *Sixty patients, aged between 20-60 years, undergoing TAH were randomly assigned into two groups each containing 30 patients, as PCEA (Group E) and multimodal analgesia (Group M). In Group E, 15 ml %0.25 bupivakain HCl and 100 µg fentanil was administered through an epidural catheter placed at L3-4 in lateral decubitus position. In all patients, anesthesia was induced with 2 mg kg^{-1} propofol and 0.5 mg kg^{-1} atracurium iv and was maintained with 70%/30% N_2O / O_2 in 1 MAC sevoflurane. Anesthesia was induced by 2 MAC sevofluran and 70% N_2O in O_2 by controlled ventilation after endotracheal intubation. Preoperative heart rate, mean arterial pressure, peripheral oxygen saturation and end tidal CO_2 levels vere recorded every 5 minutes. In Group E, 0.25% bupivacaine+100 µg fentanyl in 15 ml was injected epidurally from L3-L4 intervertebral space preoperatively and 0.25% bupivacaine+3µg/ml fentanyl solution was infused epidurally with a rate of 10 ml h^{-1} peroperatively. In the recovery room, epidural patient-controlled analgesia (basal infusion 5 ml h^{-1}, bolus 4 ml, lockout time 15 min) was started with 0.125% bupivacaine+3 µg ml^{-1} fentanyl solution. In Group M, lornoxicam 16 mg, dexamethasone 8 mg and paracetamol 1g iv were administered during induction and the surgeon infiltrated the incision with 20 ml of 0.25% bupivacaine at the end of the operation. At the recovery room, iv meperidine patient-controlled analgesia (10 mg ml^{-1}) (1.5 ml bolus dose, 8 min lockout time) was started and paracetamol 1g three times a day and lornoxicam 16 mg twice a day iv were administered. Postopeatively, visual analogue scale (VAS) scores, additional analgesic requirement, side effects, gastrointestinal system (GIS) functions (time to first bowel sound, time to first defecation), mobilization time and discharge time were recorded.*

Results: *There was no significant difference in mean arterial blood pressure, heart rate, VAS scores, additional analgesic requirement, side effects, time to first bowel sound, first mobilization and discharge time between the groups ($p>0.05$). In Group E, time to first defecation was significantly earlier than those of Group M ($p<0.05$).*

Conclusion: *In patients undergoing TAH, multimodal analgesia (iv meperidine PCA, lornoxicam, paracetamol, dexametasone and wound infiltration) provides equivalent analgesic effect and can be an alternative to epidural analgesia, although the time to first defecation was found to be earlier with epidural PCA.*

KEY WORDS: *Postoperative analgesia; multimodal analgesia; patient controlled analgesia; total abdominal hysterectomy*

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INTRODUCTION

Despite the development of new analgesic agents and techniques in recent years, almost 80% of patients undergoing major surgery still experience acute moderate-to-severe pain in the postoperative period. Inadequate postoperative pain control may both prolong the time to regain normal physiological functions and lead to a delay in overall recovery increasing morbidity and mortality and reducing the quality of life (1). The single-agent treatment is one of the main reasons for failure in the management of the postoperative pain. Even the most potent opioid analgesics when used solely cannot elliminate postoperative pain with various neurophysiological and neurochemical mechanisms (2).

The ideal postoperative pain management should be effective for not only static but also dynamic pain to reduce the surgical stress response, shorten the length of hospital stay and have a low rate of side effects and complications. Recently multimodal analgesia has been approved as ideal analgesic method following major surgeries (3). Multimodal analgesia is a method based on the principle of achieving effective analgesia and decreasing the incidence of side-effects with analgesic agents or methods via different mechanisms of action in lower doses as a result of their additive or synergistic effects (4). Strong opioids are combined with nonsteroidal antiinflammatory drugs (NSAIDs) and/or adjuvant analgesics such as capsaicin, gabapentin, ketamine, pregabaline, dexmedetomidine or tapentadol. Steroid injections and local anesthetic infiltrations can be added in order to increase the effectiveness of the treatment as well (5).

Patient-controlled epidural analgesia is a commonly used and the most effective method of pain relief after intra-abdominal surgeries. As a result of the invasive nature of the procedure, the risk of complications is high. Besides the common side effects such as motor block of the lower extremity, urinary retention, nausea-vomiting and pruritus, it also has potential complications associated with the technique like epidural haematoma, epidural abscess and neural damage (6,7). However, the results of the studies evaluating the effects of epidural analgesia on postoperative mortality, morbidity and hospital discharge are contraversial (8,9).

The aim of our study was to compare the postoperative pain scores, additional analgesic requirement, time to first bowel sound, defecation, mobilization, hospital discharge and side effects of PCEA and multimodal analgesia (iv PCA, iv paracetamol, iv lornoxicam, iv dexamethasone, infiltration of local anesthetic agents) in patients undergoing TAH.

MATERIAL AND METHOD

Following the approval of the Ministry of Health Pharmaceuticals and Pharmacy Ethics Committee, 60 patients, aged between 20-60 years, undergoing elective total abdominal hysterectomy were included in this study. Patients were randomly assigned in two groups (n=30) as epidural PCA (Group E) and multimodal analgesia (Group M). Randomisation was performed using sequential sealed envelopes in which the group names were written. Patients with bleeding diathesis, hepatic or renal dysfunction, anticoagulant therapy, a skin infection at the puncture site, neurological disorders, history of allergy to local anesthetics and other drugs, history of chronic use of analgesics as well as non-cooperative patients were excluded. All patients were informed about the study protocol on the day before the surgery and written consents were obtained.

All the patients were premedicated with 0.5 mg atropine and 0.05 mg kg^{-1} midazolam im one hour before surgery. The heart rate (HR), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2) peroperatively monitored and endtidal carbondioxide pressure ($ETCO_2$) was monitored after endotracheal intubation and all parameters recorded at 5 min intervals. General anesthesia was induced with propofol 2 mg kg^{-1} and atracurium 0.5 mg kg^{-1} iv. After endotracheal intubation, anesthesia was maintained with 1 MAC sevoflurane and 70% N_2O in oxygen.

In Group E, the epidural space preoperatively approach between L3-L4 intervertebral space, with a 18-gauge Tuohy needle, using the "loss of resistance to saline" technique and 0.25% bupivacaine+100 µg fentanyl in 15 ml was injected into the epidural space. An epidural catheter was inserted and was left 5 cm in the epidural space. No test dose was used. The level of sensory block was checked with bilateral "pin-prick" test. The target dermatome for sensory block was T6. The degree of motor block was assessed using a modified Bromage scale (0: No motor block, 1: Able to move knees and feet, 2: Able to move joint of ankle only, 3: complete motor block, unable to move lower limbs). Peroperatively, 0.25% bupivacaine+3 µg ml^{-1} fentanyl solution was infused epidurally at a rate of 10 ml h^{-1}. In the recovery room, PCEA with 0.125% bupivacaine+3 µg ml^{-1} fentanyl solution was started with 5 ml h^{-1} basal infusion, 4 ml bolus dose and 15 min lockout time.

In Group M, 16 mg lornoxicam, 8 mg dexamethasone and 1 g paracetamol iv were administered during induction. At the end of the operation, the surgeon infiltrated the incision with 20 ml of 0.25% bupivacaine. In the recovery room, after a loading dose of iv meperidine

iv patient-controlled analgesia with meperidine (10 mg ml^{-1}) was started with a bolus dose of 1.5 ml and lockout time of 8 min. 1 g paracetamol three times a day and 16 mg lornoxicam twice a day were also administered in the postoperative period.

Postoperative pain was assessed using a 100 mm VAS (0: no pain, 100: worst pain imaginable). The patients received 4 ml bolus dose via PCA when the VAS score was above 30. Postoperative follow-up was performed at 2-hour intervals during the first 8 hours, at 4-hour intervals during the next 8 hours and then at 6-hour intervals. Mean arterial pressure, heart rate, respiratory rate, VAS scores (at rest and during motion), additional analgesic requirement and side effects (nausea, vomiting, motor block, urinary retention, pruritus, sedation, respiratory depression) were recorded during the postoperative 48 hours. Also the time of first bowel sounds, defecation, mobilization and hospital discharge were recorded.

Statistical Analysis

Results were presented as mean ± SD. Paired sample t test, two-way ANOVA and post-hoc Tukey Kramer tests were used for the analysis of the repeated measurements. Chi-square test and Fisher's exact tests were used to compare the proportional data. A p value less than 0.05 was considered as statistically significant.

RESULTS

There was no significant difference in terms of the demographic characteristics of patients and the duration of surgery between the groups (p>0.05) (Table I).

Table I: Patients' demographics and surgical time (values are mean ± SD)

	Group E	Group M
Age (year)	52.0±11.2	50.0±13.7
Weight (kg)	76.1±25.1	73.8±30.4
Height (cm)	163±12.0	162±12.0
Surgical time (min)	126.9±45.2	130.5±47.5

Peroperatively, there was a significant decrease in MAP at 15th min in Group M, and at 30th and 60th min in Group E. (p<0.05) (Table II). Heart rate decreased significantly at 30, 60 and 90th min in Group E, at 15, 30 and 60th min in Group M (p<0.05) (Table III).

Table II: Mean Arterial Pressure (mmHg) (values are mean ± SD)

	Group E	Group M
0.min **(control)**	103.7±37.4	110.7±50.5
15.min	100.1±37.6	99.5±49.4*
30.min	91.1±30.9*	97.9±39.5
60.min	86.6±23.9*	92.9±34.2
90.min	90.1 ±27.7	92.2±32.9
120.min	93.8 ± 26.5	88.0±23.8

* p<0.05 (within the groups versus control)

Table III: Heart rate (beat/min) (values are mean ± SD)

	Group E	Group M
0.min (control)	86.0 ±27.6	93.7±31.3
15.min	83.5±26.1	91.5±34.8*
30.min	78.2±20.0*	86.2±27.8*
60.min	74.5±16.3*	81.2±24.0*
90.min	71.2±17.3*	76.5±20.9
120.min	73.2±21.4	78.1±30.8

* p<0.05 (within the groups versus control)

The VAS scores did not differ significantly during the postoperative period between the groups (p>0.05) (Table IV). Three patients in Group E and 2 patients in Group M required additional analgesic boluses. There was no significant difference between the groups in terms of additional analgesic requirement (p>0.05). None of patients had leg weakness postoperatively. There was not any failed epidurals.

Nausea and vomiting were the only postoperative side effects. There was no significant difference in the incidence of nausea or vomiting between the groups (p>0.05) (Table V).

Table IV: Visual Analog Scale (mm) (mean±SD)

	Group E	Group M
0 h (control)	12.0 ±23.8	28.3 ±17.9
2 h	16.6 ±25.9	19.7 ±15.7
4 h	14.7 ±17.9	18.7 ±19.8
6 h	13.1 ±21.2	18.4 ±28.1
8 h	13.9±18.7	11.7 ±18.8
12 h	13.5 ±18.4	12.3 ±27.0
16 h	10.5 ±16.7	10.6 ±18.8
22 h	11.4 ±15.9	13.6 ±21.8
28 h	10.4 ±16.9	9.8 ±21.1
34 h	10.1 ±17.1	8.7 ±19.6
40 h	7.3 ±17.4	6.9 ±14.8
48 h	9.6 ±18.0	8.5 ±17.4

Time to first bowel sounds, mobilization and discharge did not differ between the groups. However, the first defecation occured significantly earlier in Group E than that of Group M (p=0.001) (Table VI).

Table V: Rate of nausea and vomiting

	Group E	Group M
Nausea (Yes/No)	3/27	1/29
Vomiting (Yes/No)	1/29	2/28

Table VI: Time to first bowel sound, defecation, mobilization, and discharge (h) (mean±Sd)

	Group E	Group M
First bowel sound	0.8 ± 0.5	0.8 ± 0.6
Defecation	37.6 ± 27.0¶	49.3 ± 30.9¶
Mobilization	8.3 ± 3.3	8.4 ± 3.1
Discharge	54.7 ± 11.7	55.5 ± 12.2

¶ Between groups $p<0.05$

DISCUSSION

The present study demonstrates that, in patients undergoing TAH, multimodal analgesia (iv meperidine PCA, lornoxicam, paracetamol, dexametasone and wound infiltration) provides equivalent analgesic effect and can be an alternative to epidural analgesia, although the first defecation time was found to be earlier with epidural PCA.

In the mechanism of postoperative pain, central as well as peripheral sensitization play important roles. It is important to combine the agents and methods that will supress these mechanisms in order to achieve effective postoperative analgesia (10,11). The opioid consumption was found to be reduced by 33% following peroperative and postoperative paracetamol utilization in major orthopedic surgeries (12). Another study by Wininger et al (13) on patients who had undergone abdominal laparascopic surgery, revealed that paracetamol significantly reduces the opioid consumption in opioid-containing PCA. In patients receiving intermittent iv paracetamol treatment, postoperative VAS scores were also found to be reduced and fewer side effects like nausea and vomiting were observed. In our study, although we compared the multimodal analgesia regimen including paracetamol with epidural analgesia and not with intravenous opioid analgesia, we can state that paracetamol is an important component of multimodal analgesia regimen for producing comparable pain relief with epidural analgesia.

Kehlet and Dahl (11) stated that although the combination of various analgesics has an opioid dose-sparing effect, the combination was found to be ineffective in reducing the side-effects. Jin and Chung (14) also claimed that although multimodal analgesia is effective in postoperative pain relief they do not make a significant contribution to the postoperative healing process. It was straightforward to anticipate certain advantages following the utilization of multimodal analgesia but many studies failed to demonstrate these advantages. For instance it was shown that NSAID and paracetamol reduced the opioid demand from 40% to 20% but a similar decrease in side effects of opioids was not observed (15-17). In our study, we administered opioids intravenously in the multimodal analgesia group and epidurally in the epidural analgesia group. The incidence of nausea or vomiting did not differ significantly between groups. However, as we did not have a control group having intravenous opioids without NSAID or paracetamol, and the incidence of nausea-vomiting is known to be higher with intravenous opioid administration, we can not comment on the effect of these agents on the incidence of side effects of intravenous opioids.

On the other hand, in another study led by Dorr et al. (18) continuous epidural analgesia versus multimodal analgesia composed of femoral nerve block, iv ketorolac and hydromorphone were utilized in 70 patients who undergoing knee arthroscopy. It was reported that the side-effect ratio was lower in the group receiving multimodal analgesia.

In a study by Turan et al. (19), designed to compare multimodal analgesia with posterior tibial nerve block in patients underwent hallux valgus repair, it was concluded that multimodal analgesia reduced the peroperative anesthetic requirements but this effect disappeared after 24 hours. In this study multimodal analgesia was applied to patients with history of elective coronary and/or valvular surgery. The drugs used in this study did not cause any change in hemodynamic parameters when applied to patients with stable hemodynamics (20).

Chilvers et al. (21) conducted a study to compare 54 patients receiving multimodal analgesia with 59 patients receiving epidural analgesia. It was reported that an equivalent level of analgesia was achieved with both methods but the period of time needed for induction of anesthesia, the duration of stay in postoperative care unit and the average time interval from admission until discharge from hospital were found to be shorter when multimodal analgesia was applied. They also stated a reduction in the incidence of major complications. Although the multimodal analgesia regimen of our study differs from the above mentioned study of Chilvers et al. as we did not administer ketamine, clonidine and tramadol but used wound infiltration and dexamethasone in the multimodal analgesia group, we also observed that our multimodal analgesia regimen produced comparable pain relief. However, no major complications such as respiratory depression, epidural abscess, pneumonia, delirium and venous thromboembolism which were stated in the study of Chilvers et al., were observed in our study. We did not compare the period of time needed for induction of anesthesia in our study as we

had a separate "regional anesthesia" room in which we applied epidural analgesia before the surgery. A regional anesthesia room prevents the "time-consuming effect" of epidural anesthesia.

The efficiency of epidural analgesia is obvious, however there are some concerns regarding its recognition as the optimal modality. In a study by Marret et al. (22), designed to compare epidural analgesia and parenteral opioid application in patients expecting colorectal surgery, it was reported that epidural analgesia reduced the frequency of ileus formation and postoperative complication rate but had no influence on the duration of hospital stay. Moreover the researchers argued that it can eventually increase the duration of stay due to certain complications including epidural hematoma and abscess formation. The rate of anastomotic leakage formation, which is another important complication of colorectal surgery, was found to be similar in both epidural analgesia and multimodal analgesia groups. In our study the only difference was the earlier occurence of first defecation in the epidural analgesia group.

It was shown in previous studies that in postoperative period the analgesic requirement and pain can be significantly reduced with infiltration of local anesthetics on the incision site (23-25). In our study, the surgeon infiltrated the incision site with bupivacaine in multimodal analgesia group. Adjuvant analgesics play also an important role in multimodal analgesia. Although different agents with various mechanisms of action are used for this purpose, in recent years the research on corticosteriods has intensified. Dexamethasone produced a significant reduction in postoperative vomiting in various studies (26, 27), on the other hand betamethasone was found ineffective to prevent nausea and vomiting (28). In our study a reduction in the postoperative nausea and vomiting rate could not be detected in the multimodal analgesia group following a single dose of dexamethasone during the induction phase.

In this study, the wound infiltration approach and various agents including dexamethasone, lornoxicam and paracetamol, which exhibit different mechanisms of action, are applied together in order to produce multimodal analgesia. In other studies with similar purpose usually two agents or methods are utilized together and contraversial outcomes are reported as a result of the inability to inhibit all components of the postoperative pain. However, in our study four different agents and two distinct modalities are used together which presumably provided an analgesic effect equivalent to the epidural analgesia method.

Although the time to first defecation was earlier in total abdominal hysterectomy patients receiving epidural PCA, the multimodal analgesia method composed of iv meperidine PCA, lornoxicam, paracetamol and wound infiltration is able to produce an equivalent level of analgesia in these patients. Thus the multimodal analgesia application is regarded as an alternative to the epidural analgesia method.

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