The Effect of Preemptive Lornoxicam, Paracetamol and Paracetamol Lornoxicam Combinations on the Quality of Patient-Controlled Analgesia After Abdominal Surgery

Abdominal Cerrahi Geçiren Hastalarda Preemptif Lornoksikam, Parasetamol ve Parasetamol+Lornoksikam Kombinasyonunun Hasta Kontrollü Analjezi Kalitesine Etkisi

Preemptif Lornoksikam, Parasetamol ve Kombinasyonları / Preemptive Lornoxicam, Paracetamol and Combinations

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Özet

Amaç: Abdominal cerrahi geçiren hastalarda preempitif i.v. parasetamol, lornoksikam ve kombinasyonlarının ameliyat sonrası 'Hasta Kontrollü Analjezi' (HKA) ile oluşturulan analjezi kalitesi, toplam fentanil dozu ve yan etkileri araştırıldı. Gereç ve Yöntem: Atatürk Üniversitesi Tıp Fakültesi Etik Kurul onayı alınarak, ASA (American Society of Anesthesiologists) I-II, 18-70 yaş, genel anestezi altında elektif abdominal cerrahisi (orta hat kesili operasyonlar) planlanan 120 hasta randomize olarak dört gruba ayrıldı. Tüm olgulara anestezi indüksiyonu 2mg/kg propofol ve 0.6mg/kg rokuronyum ile sağlandı. Anestezi idamesi %60 azotprotoksit - %40 O2, %1–1.5 sevofluran ile sürdürüldü. Grup C (GC, n=30): İntravenöz HKA ile fentanil uygulandı. Grup L(GL, n=30): Entübasyondan yaklaşık 30 dk önce bitmek üzere toplam 1 kez iv 8mg lornoksikam verildi. Grup P (GP, n=30): Entübasyondan 30 dakika önce ve 6 saatte bir toplam 4 kez iv 1gr paracetamol verildi. Grup PL (GPL, n=30): Entübasyondan önce 1 kez iv 8 mg lornoksikam ve ilk dozu entübasyondan önce olmak üzere 6 saatte bir toplam 4 kez iv 1gr parasetamol verildi. Tüm hastalara operasyon sonrası HKA ile fentanil uygulandı. Postoperatif 2. 4. 8. 12. ve 24. saatlerde vizüel analog skala (VAS) skoru, kan basıncı-kalp hızı, sedasyon skoru, bulantı-kusma skoru, hasta memnuniyeti, yan etkiler ve toplam fentanil dozu kaydedildi. Bulgular: Postoperatif 24 saatte toplam fentanil tüketimi GC'de GP, GL ve GPL'e göre daha yüksek bulundu. 2, 8, 12, 24. saatlerde GL'de fentanil tüketimi GC'den anlamlı düşük bulundu. GPL de tüm saatlerde fentanil tüketimi GC den anlamlı düşük bulundu. Tartışma: Preemptif 8 mg lornoksikamın HKA de fentanil tüketimini azalttığını, lornoksikam ile paresetamol'ün birlikte kullanılmasının tek başına lornoksikam kullanıma üstünlüğü olmadığını gözlemledik.

Anahtar Kelimeler

Analjezi; Hasta-Kontrollü; Lornoksikam; Parasetamol; Fentanil

Abstract

Aim: We investigated total fentanyl dose, its side effects and the quality of Patient Controlled Analgesia (PCA) using preemptive paracetamol, lornoxicam and their combination after abdominal surgery. Material and Method: After approval of the Hospital Ethic Committee of Atatürk University, Erzurum, Turkey, The study included 120 ASA I or II, patients aged between 18 to 70 years, scheduled to undergo elective abdominal surgery (midline incision surgery). Patients were randomly divided into four groups. In all cases, anesthesia was induced with 2mg/kg propofol and 0.6mg/kg rocuronium. Anesthesia was maintained by using 1-1.5% sevoflurane in 60% 40% nitrous oxide - O2. Group control (Group C, n=30): received intravenous (i.v.) fentanyl through Patient Controlled Analgesia (PCA) Group Lornoxicam (Group L, n=30): a one-time 8mg dose of i.v. lornoxicam was added, which was completed approximately 30 minutes before intubation.; Group paracetamol (Group P, n=30): received 1g i.v. paracetamol before intubation, followed by every 6 hours for a total of four times. Group lornoxicam and paracetamol (Group PL, n=30): received 8mg i.v. lornoxicam before intubation, and 1g i.v. paracetamol before intubation every 6 hours for a total of 4 times. During the postoperative 2, 4, 8, 12 and 24 hours, visual analogue scale (VAS), sedation, and nausea-vomiting scores, patient satisfaction, incidence of side effects and total amount of fentanyl used were recorded. Results: Total postoperative fentanyl consumption was significantly higher in GC than of the other groups. At 2, 8, 12, 24. hours, fentanyl consumption was found to be significantly lower in GL than that in GC. In GPL, fentanyl consumption was significantly lower than in GC at all time points. Discussion: We observed that preemptive 8 mg lornoxicam decreased PCA fentanyl consumption but a combination of lornoxicam and paracetamol was not superior to lornoxicam alone.

Keywords

Analgesia; Patient-Controlled; Lornoxicam; Paracetamol; Fentanyl

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Introduction

Postoperative pain leads to complications that necessitate longer hospital stays. A multimodal analgesia method is preferred to manage pain caused by nociceptive and central stimulation. In multimodal analgesia, two or more drugs are used; therefore, while side effects arising from the usage of drugs at a high dosage are minimized, maximum benefit is obtained through the analgesic effectiveness of each individual drug [1,2]. The goal of preemptive analgesia is to prevent pain perception by inhibiting peripheral and central sensitization forming due to pain stimulation. The onset, continuation and recurrence stages of central sensitization should be blocked [3]. Opioid analgesics are the first choice in the treatment of postoperative pain. Opioid use creates anxiety due to its potential to cause respiratory depression, sedation, high levels o itching, nausea, vomiting, constipation and dependency. In order to reduce or eliminate these side effects, minimization of opioid dose has been advocated [4]. Paracetamol and NSAI drugs are well known for their effectiveness and have good safety profiles. Their individual use or combinations with opioids provide effective pain control for postoperative pain management [5,6]. The exact action mechanism of paracetamol has not been completely explained, however, it is thought to have an indirect effect on the serotonergic system through central COX3 inhibition of the central nervous system (CNS) [7]. The mode of action for lornoxicam consists of the suppression of COX1 and COX2 isoenzymes, which inhibits the synthesis of inflammation mediators, prostaglandins [8]. Our goal is to provide more effective analgesia through the combination of antinociceptive effects that develop in different ways. The present study investigated the effects of preemptive i.v. paracetamol, i.v. NSAI and their combinations on the quality of Patient Controlled Analgesia, total fentanyl dose and side effects in patients who had abdominal surgery under general anesthesia.

Material and Method

Following the approval of the Ethics Committee of Atatürk University Hospital and patient consent, this study included 120, ASA I-II patients between the ages of 18-70, who were planned to have abdominal surgery under general anesthesia. Patients who had concomitant illnesses such as diabetes mellitus, hypertension and psychosis, and those who had a history of antiemetic, antihistamine, analgesic or corticosteroid use in the previous 24 hours were excluded from the study. The patients were monitored using electrocardiography (ECG), finger oxygen saturation (SpO2) and non-invasive arterial pressure. Anesthesia induction was provided with 10 L min-1 of 100% oxygen and 2 mg kg-1 of propofol (Propofol 2% Fresius®, Fresenius Kabi, Sweden) administered 3 minutes after pre-oxygenation. Anesthesia maintenance was achieved using 40% O2, 60% N2O and 1-1.5% sevoflurane (Sevoflurane liquid®, Abbott, U.K.). Endotracheal intubation was established with 0.6 mg kg-1 of rocuronium bromide (Esmeron® 50 mg, Organon, Holland) and maintained with 0.1 mg kg1 rocuronium bromide, administered as required. Preoperative and intraoperative opioids were not given to any patient. In this randomized, prospective and double-blind study, patients were randomly divided into 4 groups of 30 people. Group Control (GC, n=30); In addition to the Patient Controlled Analgesia method, 100 ml of i.v. 0.9% NaCl was administered every 6 hours as placebo with the condition that the initial dose was finished 30 minutes before intubation.

Lornoxicam group (GL, n=30); a one-time 8mg dose of i.v. lornoxicam (Xefo®; 8mg/2ml Nycomed Pharma AS, Roskilde, Denmark) was added, which was completed approximately 30 minutes before intubation. Paracetamol group (GP, n=30); with the initial dose completed 30 minutes before intubation, 1 g of i.v. paracetamol (Perfalgan®, Bristol-Myers Squibb, France) was administered every 6 hours, for a total of 4 times. Lornoxicam and paracetamol group (GPL, n=30); a one-time 8 mg dose of i.v. lornoxicam completed approximately 30 minutes before intubation, and with the initial dose completed 30 minutes before intubation, 1 g of i.v. paracetamol was administered every 6 hours for a total of 4 times. Paracetamol administration was conducted in the form of an infusion with in 15 minutes. Immediately after the operation, fentanyl (loading dose of 1.5 µg·kg-1 fentanyl, bolus dose of 25 µg, 10 minute lock-out interval, 4 hour limit of 400 µg) was initiated in all groups with a PCA instrument (Abbott Pain Management Provider, North Chicago, IL), in the recovery room. Patients were kept in the recovery room for 1 hour after intubation and then transferred to the clinic at the end of the hour. VAS score, blood pressure and heart rate, sedation score, nausea-vomiting score and patient satisfaction scales of the patients were recorded at 2,4,8,12 and 24-hours postoperatively. Side effects (itching, nausea-vomiting, sedation, respiratory depression) and total fentanyl use were recorded. Pain intensity was evaluated using a visual analogue scale consisting of a 10 cm long, graded horizontal line which had “no pain” written on the left end, and “worst pain possible” written at the right end. Sedation was evaluated with a 4-point scale: 1=awake, eyes open; 2=drowsy, can be awakened easily with verbal stimulation; 3=drowsy, difficult to awaken; 4=drowsy, can not be woken by shaking. Nausea and vomiting were evaluated on a 3-point scale: 0=Nausea and vomiting not present; 1=Nausea; 2=Retching; 3=Vomiting. Retching was considered vomiting. Patients who experienced more than one episode of vomiting or retching within 30 minutes received 10 mg of metoclopramide (Metpamide® 10mg, Yeni, İstanbul).

Results were analyzed with SPSS statistical program (Version 15.0, SPSS Inc., Chicago, IL, USA). One Way analysis of variance (ANOVA) was used for between-groups comparison of age, weight, and VAS, fentanyl consumption, sedation score, incidence of side effects, and patient satisfaction. The chi-square test was used for the comparison of groups hour values. Preemptive paracetamol, NSAIDs and combination of both drugs were reduced the dose of fentanyl at the end of 24 hours. We considered the reduced the amount of fentanyl dose as the primary outcome. Power analysis determined that 24 patients would be required in each group to detect a 25% difference in the amount of fentanyl used in the 24 h postoperative period with a power (1- ß) of 0.8 (α = 0.05). The Bonferroni approach was used for multiple comparisons, with a value of α= 0.013 for the four groups.

Results

No statistically significant difference was found between the groups based on age, sex, weight, operation duration, or bolus

Table 1. Demographic Characteristics and Operation Time (mean ± SD).

	Group P (n=30)	Group L (n=30)	Group PL (n=30)	Group C (n=30)	p-value
Sex (F/M)	19/11	22/8	19/11	17/13	0.613
Age (year)	48.86 ± 11.28	47.33 ± 14.78	51.30 ± 12.90	50.20 ± 12.40	0.664
Weight (kg)	68.23 ± 14.84	67.16 ± 13.20	70.33 ± 12.42	73.40 ± 14.83	0.322
Operation time (min)	145.66 ± 40.69	143.50 ± 34.16	162.33 ± 51.17	166.00 ± 48.59	0.106
Loading dose (μg)	104.66± 19.87	101.13 ± 19.20	105.33 ± 18.68	109.40 ± 20.83	0.448

Data are mean ± SD or n of patients. Loading dose: after the operation fentanyl 1.5μg/kg IV in the recovery room Group P: Group Paracetamol, Group L: Group Lornoxicam, Group C: Group Control, GPL: Group Paracetamol and Lornoxicam. There were no statistically significant between – group differences.

fentanyl use (p>0.05) (Table I). No significant intergroup difference was found for non-invasive blood pressure, pulse and oxygen saturation (p>0.05). Respiratory depression, bradycardia and hypotension were not observed in any of the groups. In GC, the total fentanyl dosage consumed in 24 hours was found to be significantly higher compared to other groups (p=0.001) (Table II). At 2,8,12 and 24 hours, fentanyl consumption was determined to be significantly lower in GL compared to GC (p=0.02, p=0.008, p=0.004, p= 0.001, respectively). Fentanyl consumption was found to be lower in GPL at all time points, compared with GC (p=0.004, p=0.001, p=0.001, p=0.001, p=0.001, respectively). No significant difference was found between GC and GP at 2,4,8 and 12 hours (p>0.013). There was no significant difference between groups with regards to 2- hour VAS scores. At 4 and 8 hours postoperative, VAS scores for GC were significantly higher than GL and GPL. At 12 and 24 hours postoperative, VAS scores for GC were significantly higher than other groups (Table III). There was no significant difference in postoperative nausea-vomiting score and itching (Table IV, Table V). No significant difference was found between groups for patient satisfaction (p = 0.098) (Table- VI).

Table 2. Fentanyl levels between the groups (mean ± SD).

Time	Group P (n=30)	Group L (n=30)	Group PL (n=30)	Group C (n=30)	p-value
2. hour	220.46 ± 48.11	200.30 ± 54.09	192.16 ± 82.57	246.93 ± 53.97&	0.004
4. hour	372.76 ± 108.09	344.30 ± 85.71	293.50 ± 145.91	408.60 ± 90.34	0.001
8. hour	548.60 ± 126.18	507.70 ± 141.26	416.16 ± 146.15	625.60 ± 147.07&	0.001
12. hour	695.56 ± 130.45	658.16 ± 205.11	578.16 ± 151.34	811,00 ± 182.47&	0.001
24. hour	894.40 ± 172.34	858.06 ± 192.88	845.16 ± 133.80	1070.46 ± 171.77**	0.001

Data are mean±SD. Fentanyl dose (μg). Group P: Group Paracetamol, Group L: Group Lornoxicam, Group C: Group Control, Group PL: Group Paracetamol and Lornoxicam. + significant differences from Group C and Group P, &significant differences from Group L and Group PL, ** significant differences from other groups.

Through this method, the analgesic effect of each agent is utilized at the highest level, while the effects arising from high doses are reduced [9]. Preemptive analgesia by various methods recommended for treatment of postoperative pain. İnal et al. recommended the usage of preemptif TAP block for early postoperative pain management as an adjunct to multimodal analgesia [10]. In a study by Aydoğan et al. the use of meperidine with preemptive paracetamol was reported to be ineffective [11]. Similarly, in cardiac surgery patients, Cattabriga et al. added paracetamol to tramadol before the end of the operation [12]. In the group that had paracetamol added, VAS score and morphine use showed a non-significant reduction. In a study by Remy et al. where morphine was administered through PCA, and oral or i.v. acetaminophen was given in addition to morphine; with the addition of acetaminophen, average morphine consumption decreased by 20% in a 24 hour period; nausea-vomiting, itching incidences did not change; sedation score decreased by 18%; and no significant change was reported in VAS score and patient satisfaction [13]. In previous studies and meta-analyses investigating the effect of paracetamol use on side effects, opioid consumption and postoperative patient satisfaction, paracetamol was observed to reduce the use of opioids; however, it did not affect the incidence of side effects related to opioids [14,15]. In our study, where paracetamol was also given preemptively, it reduced total fentanyl consumption in a 24 hour period; however, there was no statistical signifi-

Table 3. VAS Score

Time	Group P (n=30)	Group L (n=30)	Group PL (n=30)	Group C (n=30)	p-value
2. h	4.86 ± 1.16	4.66 ± 1.62	4.63 ± 1.09	4.96 ± 1.07	0.042
4. h	4.30 ± 0.98	4.00 ± 1.08	3.76 ± 0.81	4.70 ±1.05*	0.003
8. h	3.46 ± 1.25	3.66 ± 1.25	3.36 ± 0.96	4.20 ± 0.84*	0.015
12.h	3.30 ± 1.14	3.26 ± 1.01	2.80 ± 0.71	4.06 ± 0.63*	0.001
24. h	2.90 ± 0.95	2.90 ± 0.92	2.43 ± 0.67	3.66 ± 0.92*	0.001

VAS: Visual Analogue Scale, Data are mean±SD. Group P: Group Paracetamol, Group L: Group Lornoxicam, Group C: Group Control, Group PL: Group Paracetamol and Lornoxicam. *Significant differences from other groups.

Discussion

Multimodal analgesia reduces the incidence of opioid related side effects. Sufficient analgesia can be achieved by creating additive or synergistic effects through different analgesics.

Table 4. Postoperative Nausea and Vomiting Score 4.h

Nausea and Vomiting Score	Group P (n=30)	Group L (n=30)	Group PL (n=30)	Group C (n=30)
0	23 (76.7)	24 (80)	24 (80)	24 (80)
1	4 (13.3)	5(16.7)	3(10)	2(6.7)
2	1(3.3)	0 (0)	0 (0)	1(3.3)
3	1(3.3)	0 (0)	3 (10)	0 (0)

Data are n(%) of patient. Group P: Group Paracetamol, Group L: Group Lornoxicam, Group PL: Group Paracetamol and Lornoxicam, Group C: Group Control. 0=Nausea and vomiting not present, 1=Nausea, 2=Retching, 3=Vomiting. There were no statistically significant between – group differences (p=0.813).

Table 5. Postoperative Nausea and Vomiting Score 24.h

Nausea and Vomiting Score	Group P (n=30)	Group L (n=30)	Group PL (n=30)	Group C (n=30)
0	25 (83.3)	29 (96.7)	25 (83.3)	26 (86.7)
1	3 (10.0)	1 (3.3)	2 (6.7)	4 (13.3)
3	2 (6.7)	0 (0)	3 (10)	0 (0)

Data are n(%) of patient. Group P: Group Paracetamol, Group L: Group Lornoxicam, Group PL: Group Paracetamol and Lornoxicam, Group C: Group Control. 0=Nausea and vomiting not present, 1=Nausea, 2=Retching, 3=Vomiting. There were no statistically significant between – group differences (p= 0.172).

Table 6. Patient Satisfaction Level

Patient Satisfaction	Group P (n=30)	Group L (n=30)	Group PL (n=30)	Group C (n=30)
1	0 (0)	0 (0)	0 (0)	0 (0)
2	0 (0)	0 (0)	0 (0)	0 (0)
3	5 (16.7)	0 (0)	0 (0)	3 (10)
4	25 (83.3)	30 (100)	30 (100)	27 (90)

Data are n(%) of patient. Group P: Group Paracetamol, Group L: Group Lornoxicam, Group PL: Group Paracetamol and Lornoxicam, Group C: Group Control. 1: not satisfied, 2:moderately dissatisfied, 3: significantly satisfied, 4:completely satisfied. There were no statistically significant between – group differences (p = 0.098).

cance at other time points. With regard to side effects, similar to previous findings, preemptive paracetamol did not produce a difference, compared to the control group.

Karaaslan et al. administered preemptive 100 and 200 mg celecoxib during total abdominal hysterectomy; morphine consumption in the control group was found to be higher compared to the other groups and they reported that 100 mg of celecoxib was sufficient for preemptive analgesia [16]. In gynecological operations, Tolu et al. administered 8 mg preemptive lornoxicam and used PCA with epidural morphine to establish postoperative analgesia [17].

When compared to the placebo group, the group that received preemptive lornoxicam needed analgesia later; in the lornoxicam group, total morphine amount in 24 hours was low; and no difference was found between groups based on side effects and surgical stress. Karaman et al.

reported that, in major abdominal surgery, preemptively administered i.v. lornoxicam increased analgesia quality, decreased VAS scores and tramadol consumption, and there was no difference between groups based on nausea-vomiting [18]. Işık et al. reported that, in lumbar disc surgery, preemptive lornoxicam doses of 8 and 16 mg both reduced the amount of pethidine hydrochloride consumed during 24 hours; however, there was no significant

difference between the two doses [19]. While no difference was found between groups based on VAS score analysis at 2 and 4 hours, VAS scores of the control group at 6 and 24 hours were found to be significantly higher compared to the other two groups. Nausea-vomiting rates were 20% in the placebo group, 35% in the 8 mg lornoxicam group, and significantly higher, at 60%, in the 16 mg lornoxicam group. In our study, fentanyl consumption at 2, 8, 12 and 24 hours was found to be lower in the group that received 8 mg of preemptive lornoxicam, compared to the control group. While there was no significant variation between VAS scores at 2 hours postoperatively, at 4,8 and 12 hours, VAS scores were significantly lower compared to the control group. Many factors play a role in the etiology of postoperative nausea-vomiting, especially factors such as the waste effect of anesthetic gases and surgical procedures. However, opioids are one of the most important factors in increasing the incidence of postoperative nausea-vomiting. In our study, we postulate that the higher rate of nausea-vomiting in patients who received lornoxicam in the early postoperative period, compared to the fentanyl group, may be due to the commonly observed NSAI side effects related to the gastrointestinal system; in addition, increased nausea-vomiting in the control group during the late postoperative period may be related to the increased cumulative opioid dose.

Due to the analgesic, antipyretic and anti-inflammatory properties of NSAI drugs compared to other analgesic drugs, they provide additional advantages for patients who undergo operations. Lornoxicam is the preferred NSAI drug because of its rapid onset of action and short half-life. In a study by Trampitsch et al., 66 patients who were planned to have a gynecological operations were divided into 3 groups; 8 mg of i.v. lornoxicam was administered every 8 hours before the operation to the first group, and before the end of the operation to the second group [20]. The third group received a placebo during the pre-operative period and before the end of the operation. Compared with the other two groups, morphine consumption was significantly lower in the group that was given lornoxicam before the operation. In conclusion, it was determined that preemptive lornoxicam used in gynecological operations improved analgesia quality and reduced opioid consumption. Şencan et al. Applied 8 mg lornoxicam and 100 mg tramadol preemptively during abdominal hysterectomy [21]. They found no significant difference in the time of initial analgesia requirement and total analgesic consumption, and preemptive lornoxicam and tramadol were equivalent. In our study, we also determined that 8 mg of lornoxicam reduced the amount of opioids consumed and, with opioid analgesics, it was effective in the management of moderate to severe pain.

In lumbar disc hernia operations, upon closing of the wound, Dilmen et al. administered 1g of methimazole or 1 g of paracetamol or 8 mg of lornoxicam [22]. No difference was observed between groups regarding postoperative nausea-vomiting, antiemetic requirement, itching or respiratory rate. During the 24-hour follow-up, pain scores decreased in the methimazole and paracetamol group, however they did not decrease in the lornoxicam group. Although morphine consumption in the paracetamol group decreased over time, no difference was found between groups in terms of total morphine consumption within 24 hours. In our study, we observed reduced fentanyl consumption in the group that received preemptive lornoxicam, compared to the control group and also the group that received

preemptive paracetamol. In contrast to our study, Dilmen et al. did not use lornoxicam preemptively, which might account for the differing results. In the present study, fentanyl consumption was lower in the combined paracetamol and lornoxicam group than the lornoxicam group, but this difference was not statistically significant. Also, the use of lornoxicam in combination with paracetamol was not superior to the use of lornoxicam alone. İn conclusion, we believe that preemptive lornoxicam is an effective drug in multimodal analgesia; the use of lornoxicam in combination with paracetamol does not increase efficacy and further studies are necessary.

Competing interests

The authors declare that they have no competing interests.

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