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ORIGINAL ARTICLE

Effects of peroperative intravenous paracetamol and lornoxicam for lumbar disc surgery on postoperative pain and opioid consumption: A randomized, prospective, placebo-controlled study

Lomber disk cerrahisi için peroperatif intravenöz parasetamol ve lornoksikamın postoperatif ağrı ve opioid tüketimine etkileri: Randomize, prospektif plasebo kontrollü bir çalışma

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Summary

Objectives: The aim of the present randomized, placebo-controlled study was to compare postoperative analgesic effects of peroperative paracetamol and lornoxicam administration.

Methods: Sixty adult patients with American Society of Anesthesiologists (ASA) risk classification I-II, who would undergo single-level lumbar discectomy under general anesthesia, were enrolled. Patients were administered either 1000 mg paracetamol (Group P), 8 mg lornoxicam (Group L), or saline (Group C) prior to induction of anesthesia (n=20 for all groups). All patients were administered the same anesthesia induction and maintainance. Postoperative analgesia was maintained with the same analgesic drug in each group. Rescue analgesia was supplied with intravenous meperidine delivered by a patient-controlled analgesia device. Numeric rating score (NRS) results, first analgesic demand time, and cumulative meperidine consumption were recorded postoperatively. Primary outcome was NRS at first postoperative hour. Secondary outcome was measure of opioid consumption during first 24 postoperative hours.

Results: At first postoperative hour, NRS of Group L [4 (0-8)] was lower than NRSs of Groups P and C [6(0-7); 6(0-9), respectively; p<0.016]. Time to first analgesic demand of Group L was longer, compared with those of the other groups (p<0.016). Cumulative postoperative meperidine consumption in Group L was less than those of Groups P and C at 2-, 12-, and 24-hour time intervals (p<0.016), while Groups P and C had similar findings for the same time intervals.

Conclusion: Preoperative lornoxicam administration decreased early postoperative pain scores more effectively than paracetamol.

Keywords: Lumbar disc surgery; paracetamol; lornoxicam; postoperative pain; patient-controlled analgesia.

Özet

Amaç: Bu randomize plasebo kontrollü araştırmanın amacı peroperatif lornoksikam ve parasetamol kullanımının postoperatif analjezik etkilerini karşılaştırmaktır.

Gereç ve Yöntem: ASA I-II risk grubunda tek seviye lomber diskektomi yapılması planlanan 60 hasta çalışmaya alındı. Hastalara 1000 mg parasetamol (Group P), 8 mg lornoksikam (Grup L) veya salin (Grup S) uygulandı (her grupta n=20). Tüm hastalarda aynı anestezi indüksiyonu ve idamesi uygulandı. Postoperatif analjezi o gruptaki analjezikle devam ettirildi. Kurtarıcı analjezik olarak Hasta Kontrollü Analjezi cihazıyla intravenöz meperidin verilmesi sağlandı. Nümerik Ağrı Skoru (NAS), ilk analjezi istek zamanı ve kümülatif meperidin kullanımı postoperatif olarak kaydedildi. Araştırmanın primer değişkeni ilk postoperatif saateki NAS olarak belirlendi. İkincil değişken olarak postoperatif 24 saatte tüketilen opioid miktarı belirlendi.

Bulgular: İlk postoperatif saatte Grup L'deki NAS [4 (0-8)], Grup P [6(0-7)] ve Grup S'deki [6(0-9)] NAS skorlarından anlamlı olarak daha düşüktü (p<0.016). Diğer gruplarla karşılaştırıldığında Grup L'deki ilk analjezik istek süresi daha uzundu (p<0.016). Kümülatif meperidin kullanımı postoperatif 2-12 ve 24. saatlerde Grup L'de diğer iki gruba göre daha azdı (p<0.016). Aynı zaman dilimlerinde Grup P ve S benzer bulgulara sahipti.

Sonuç: Preoperatif lornoksikam uygulaması erken postoperatif ağrı skorlarını parasetamole göre daha iyi düşürür.

Anahtar sözcükler: Lomber disk cerrahisi; parasetamol; lornoksikam; postoperatif ağrı; hasta kontrollü analjezi.

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Introduction

Moderate to severe postoperative pain is common after lumbar discectomies. Multimodal analgesic regimens are prescribed, and they are in common use today in order to treat postoperative pain from lumbar disk surgery. In a previous work we demonstrated that local infiltration of the surgical wound with levobupivacaine and tramadol mixture decreases the postoperative pain as a part of a multimodal analgesic regimen.[1] However, non steroidal anti-inflammatory drugs (NSAID) remain one of the cornerstones of multimodal analgesic regimens and researchers continue to explore new NSAIDs to find the best option for patients under these circumstances.[2,3]

Efficacy of NSAID in controlling postoperative pain differs according to surgical site, inflammatory processes related to surgery, preoperative medications and other factors depending on the patient.[4] Intravenous paracetamol and lornoxicam are two new drugs that were recently introduced into clinical practice.

Paracetamol is an non-opioid agent which is assumed to be effective primarily on the central nervous system through central cyclooxygenase (COX) inhibition.[5,6] It has no anti-inflammatory effect. Lornoxicam shows its effect through peripheral nocioception by inhibiting the synthesis of prostaglandins, which are inflammation mediators, by means of its stabilized and temporary inhibition of COX-1 and COX-2 iso-enzymes.[7] Although paracetamol and lornoxicam have been used previously to control postoperative pain after lumbar disc surgery, their postoperative analgesic actions were not compared when both drugs were administered preemptively.[8,9] The preemptive analgesic effect of drugs may have important contributions to the management of postoperative pain.[10]

We hypothesized that anti-inflammatory characteristics of lornoxicam could serve to provide better analgesia if it is administered preoperatively. To test this hypothesis, we evaluated paracetamol and lornoxicam's analgesic efficacy when they were administered preoperatively, and compared them with placebo. The primary outcome of the study was the Numeric Rating Score at the first postoperative hour. Secondary outcome measurement was the amount of opioid consumption in the first postoperative 24 hours.

Materials and Methods

This prospective, randomized, placebo-controlled study was conducted at Zonguldak Karaelmas University Application and Research Hospital with the consent of Zonguldak Karaelmas University Medical Faculty Ethic Council (Under the presidency of Assoc. Prof. Dr. Banu D. Gun, 26/02/2009, no: 2009/03).

Sixty patients with ASA physical status classification of I-II, aged from 18-65, and scheduled to have single distance lumbar disc surgery were enrolled in this study. Patients who gave oral and written informed consent were randomly divided into three groups using the sealed envelope method:

1. Group L: n=20, Lornoxicam group (Xefo®; 8 mg 2 ml vial, Abdi Ibrahim, Istanbul, Turkey)
2. Group P: n=20, Paracetamol group (Perfalgan®; 1000 mg 100 ml vial, Bristol-Myers Squibb)
3. Group C: n=20, Control group (Saline; 2 ml)

Patients who were allergic to any of the study drugs, with peptic ulcer, gastroesophageal reflux, non-specific gastrointestinal system complaints, central nervous system diseases, liver or renal failure, hemorrhagic diathesis and coagulation impairment, who used preoperative opioid or non-steroid analgesic, who have history of alcohol or drug addiction and who have difficulty in understanding and using the PCA device were not included in the study. Patients, who underwent major laminectomy beyond routine discectomy procedure, who developed inter-operative complications and whose surgery lasted longer than 2 hours were to be excluded from the study.

All patients were informed about the anesthesiological method to be applied in pre-operative evaluation. The patient-controlled analgesia device (Pain Management Provider, Abbott Laboratories North Chicago, IL60064, USA) and Numeric Rating Scale (NRS, 0 = none, 10 = worst pain imaginable) were introduced to the patients. Patients were premedicated with 0.05 mg/kg intramuscular midazolam (Dormicum 5 mg/5ml, Roche) before their arrival to the operation theatre.

In pre-operative preparation room, patients' ECG, heart rate (HR), systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial blood pressure (MAP) and peripheral oxygen saturation (SpO2) were monitored (Petaş KMA® 800 IEC, Turkey) and iv infusion of lactated Ringer's solution was started. Study drugs were administered according to group allocation: Group L (2 ml, 8 mg lornoxicam) iv bolus, Group P (1000 mg, 100 ml paracetamol) 15 min iv infusion, and Group S (2 ml salin) iv bolus. Presence of any local or systemic allergic symptoms and hemodynamic parameters were recorded at 5 min intervals.

Patients were taken to the operation room 45 min after the administration of the study drug. Monitoring (Datex-Ohmeda Excel 2000) continued within the operation room and anesthesia induction was completed with 2 mg/kg propofol (Propofol 1%, Fresenius, Istanbul Turkey) and 0.6 mg/kg rocuronium (Esmeron 10 mg/5ml, Organon, Istanbul, Turkey). Anesthesia was maintained with 4-6% desflurane (Suprane, Eczacıbaşı-Baxter, Istanbul) in 50-50% N2O-O2 mixture. HR, MAP and SpO2 were recorded every 5 min intraoperatively. No additional analgesic was allowed during the surgery.

After extubation, patients were evaluated with the Modified Aldrete Scoring System at PACU and the time when they had a score of 9 was accepted as time 0.[11] Where NRS score was ≥4, 0.5 mg/kg iv meperidine was administered and maintenance analgesia was supplied with iv PCA (meperidine, basal infusion 1 mg, bolus 5 mg, lock-out time 10 min, 4 hours limit 100 mg) device. The duration between extubation and meperidine administration was recorded as first analgesic request time. Subjects were sent to the ward after being observed for 1 hour in PACU after anesthesia.

Patients in Group L were administered 8 mg iv lornoxicam 12 after the first lornoxicam medication. Patients in Group P were administered 1000 mg paracetamol via infusion at the 6th, 12th and 18th hours following the first paracetamol dosage. Patients in Group C were administered an additional 2 ml saline iv, 12 hours after the first saline medication. At the 0th, 1st, 2nd, 4th, 8th, 12th and 24th post-operative hours, NRS, HR, MAP, and SpO2 were recorded. Total meperidine consumption, number of demands and given boluses were read from the PCA device and recorded. Occurrence of adverse effects such as nausea, vomiting, or epigastrical pain was recorded as either absent or present and metoclopramide was administered when necessary.

Results

All patients completed the study protocol. There were no patients who were excluded or wished to leave the study.

There was no significant difference among the groups in terms of demographic data (Table 1). In comparison among the groups, differences between pre-operative, interoperative and post-operative MAP, HR, and SpO2 values were determined to be insignificant (p>0.016).

Time to first analgesic request and meperidine consumption according to the groups, at the 2nd, 12th and 24th hours are shown in Table 2. Cumulative amount of meperidine consumption according to time is shown in Figure 1.

Table 1. Demographic data according to the groups

	Groups			p		
	Group L	**Group P**	**Group C**	**L&P**	**L&C**	**P&C**
Sex (M/F)	10 (50%)/10 (50%)	8 (40%)/12 (60%)	10 (50%)/10 (50%)	0,525 ‡	1 ‡	0,525 ‡
Age (Year)	48,500 (30-65)	53 (30-65)	50 (38-65)	0,242 £	0,461 £	0,583 £
Weight kg)	74 (53-106)	75,5 (60-105)	81 (59-102)	0,512 £	0,327 £	0,718 £
ASA (I/II)	9 (45%)/11(55%)	4 (20%)/16 (80%)	8 (40%)/12 (60%)	0,176 ‡	0,749 ‡	0,301 ‡
Operation time (min)	75 (60-105)	92,5 (60-115)	80 (55-110)	0,021 £	0,414 £	0,102 £

£: Mann Whitney U Test; ‡: Chi Square Test; Significance is accepted at p<0.016; (median (min – max))

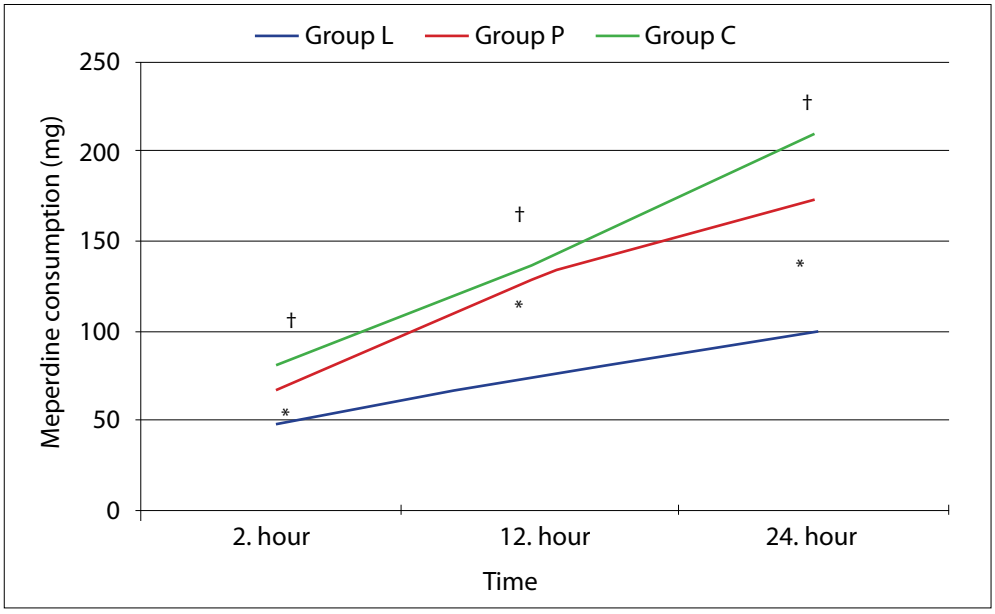

Figure 1. Mean meperidine consumption amounts according to the groups.
*p<0.016: Group L and Group P; Mann Whitney U test; †p<0.016: Group L and Group C; Mann Whitney U test

Numbers of bolus demands and given doses in the groups are shown in Table 3. There was no significant difference among the groups in terms of preoperative NRS values. Postoperative NRS scores were significantly different in comparison with the baseline only at the first postoperative hour: Group L [4 (0-8)] and Group P [6(0-7)] (p=0.018); between Group L [4 (0-8)] and Group C [6(0-9)] (p=0.004). No difference in NRS scores was determined among the groups at the other hours. Data are shown in Table 4.

In terms of adverse effects such as nausea, vomiting, or epigastrical pain, there was no significant difference between groups (p>0.016). Nausea was observed in 7 subjects in Group L, 6 subjects in Group P, and 3 subjects in Group C; and 2 subjects in Group L, 1 subject in Group P, and 1 subject in Group C needed treatment.

Discussion

In the current study we determined that preoperatively administered lornoxicam for postoperative pain treatment decreased the first postoperative NRS scores for pain and subsequent requirement and consumption of opioids were significantly better than the paracetamol and control groups.

Table 2. First analgesic request duration and meperidine consumption at the 2nd, 12th and 24th hrs according to the groups

	Group L	Group P	Group C	p		
				L&P	L&C	P&C
First analgesic request duration (min)	52,5 (5-840) *†	15 (5-210)	10 (5-240)	0,001	>0,001	0,038
Meperidine consumption at the 2nd hr (mg)	52 (0-68) *†	70 (0-100)	90 (0-100)	0,002	>0,001	0,040
Meperidine consumption at the 12th hr (mg)	74.5 (0-142) *†	116 (50-222)	136,5 (87-210)	>0,001	>0,001	0,383
Meperidine consumption at the 24th hr (mg)	98 (64-175) *†	154,5(67-330)	206 (135-308)	>0,001	>0,001	0,028

* p<0.016: Group L and Group P, Mann Whitney U Test; † p<0.016: Group L and Group C, Mann Whitney U Test; Significance is accepted at p<0.016; (median (min – max))

Table 3. Bolus demand and delivery numbers according to the groups

	Time (hr)	Group L	Group P	Group C	p		
					L&P	L&C	P&C
Bolus demand (n)	2nd hr	5 (0-12) *†	12,5 (0-50)	16 (0-35)	>0,001	>0,001	0,478
	12th hr	9.5 (0-72) *†	28 (4-91)	32 (13-160)	>0,001	>0,001	0,192
	24th hr	13.5 (2-75) *†	36.5 (4-226)	40 (25-210)	>0,001	>0,001	0,265
Delivered bolus (n)	2nd hr	2(0-6) *†	6 (0-14)	9,5 (0-12)	0,002	>0,001	0,026
	12th hr	5 (0-20) *†	12.5 (2-38)	18 (9-30)	>0,001	>0,001	0,277
	24th hr	6.5 (2-22) *†	20.5 (2-53)	25,5 (13-51)	>0,001	>0,001	0,192

* p<0.016: Group L and Group P, Mann Whitney U Test; † p<0.016: Group L and Group C, Mann Whitney U Test; Significance is accepted at p<0.016; (median (min – max))

Following lumbar discectomy, the increase of analgesia effect in the patients who were administered analgesic and steroids together has shown that inflammation has a significant role in the control of postoperative pain in these patients.[14] Thus, NSAIDs are widely used for such postoperative pain especially where bone and soft tissue inflammation are present.[15-20] Although the non-opioid to be used has less analgesic effect than the opioid, when inflammation is one of the underlying reasons for the pain, their results can be as good as opioid therapy and they can increase the effectiveness of opioids.[4,14,20]

However NSAIDs lead to gastrointestinal damage, they have renal toxicity risk, and they have been held responsible for the increase in hemorrhage after surgery, thus increasing the interest in other analgesic agents. Paracetamol is a drug which is widely used around the world in oral form with its low gastrointestinal adverse effect profile and its analgesic and antipyretic effectiveness known for a long time. After being introduced in parenteral form, it has also been used in postoperative pain treatment. However, paracetamol is an analgesic which has no anti-inflammatory effect.

In our study, NRS values in Group L in the first postoperative hour and the NRS values in Groups P and C were observed to be low and we found that this was statistically significant. Good analgesic efficacy with lornoxicam for lumbar disc surgery has been demonstrated before.[21,22] Thus we attribute our results to the better analgesic effectiveness of lornoxicam compared to paracetamol in the early post operative period.

Table 4. NRS scores according to the groups

NRS Scores	Group L	Group P	Group C	p		
				L&P	L&C	P&C
Preoperative	6,5 (4-8)	7 (5-9)	7,5 (5-9)	0,461	0,108	0,314
0. h	4(0-8) †	6(0-7)	6(0-9)	0,018	0,004	0,478
1. h	1 (0-6)	1 (0-4)	0,5 (0-3)	0,602	0,445	0,758
2. h	1 (0-4)	0 (0-3)	1 (0-3)	0,383	0,718	0,529
3. h	0 (0-2)	0 (0-5)	1 (0-2)	0,989	0,096	0,157
4. h	0 (0-2)	0 (0-3)	0,5 (0-7)	0,758	0,201	0,429
6. h	0 (0-2)	0 (0-4)	0,5 (0-3)	0,968	0,327	0,398
8. h	0 (0-2)	0 (0-5)	1 (0-3)	0,659	0,142	0,157
12. h	0 (0-3)	0 (0-3)	0 (0-1)	0,925	0,547	0,602
24. h	0 (0-5)	0 (0-3)	0 (0-3)	0,989	0,968	0,968

† p<0.016: Group L and Group C; Mann Whitney U Test; Significance is accepted at p<0.016; (median (min – max))

Isik et al.[22] determined that preemptive administration of lornoxicam has analgesic effectiveness in the early post-operative period after lumbar disc surgery. The results of our study are in parallel with this earlier study. Similarly, Toygar et al.[8] were also unable to show an early postoperative analgesic effect with paracetamol for lumbar disc surgery patients. O'Hanlon et al.,[19] Zor et al.,[23] and Gilberg et al.[24] determined that the first analgesic requirement of preemptive groups occurred later, their pain scores were lower, opioid consumption was little and postoperative analgesic quality was better in their studies in which they evaluated preemptive and postoperative NSAIDs. The longer duration for first analgesic request that we observed in Group L might be a consequence of pre-emptive lornoxicam's extending the analgesic effect in the post-operative period. On the other hand, the statistical difference between first analgesic requirement times of Groups P and C do not seem clinically significant. The first analgesic requirement time was found to be 38 minutes for 4 mg lornoxicam and 100 minutes for 8 mg lornoxicam in the study conducted by Rosenow et al.[25] The difference in first analgesic request time of Rosenow and our study may arise from different surgical procedures and lornoxicam administration methods.

In a recent study, Korkmaz Dilmen et al.[9] compared lornoxicam, paracetamol, and metazimol and placebo administration for post-operative analgesia in lumbar disc hernia. However they started to administer analgesic drugs post-operatively and provided postoperative analgesia with morphine PCA. They found that lornoxicam's effect on post-operative opioid consumption was similar to placebo.[9] The same researchers also found that paracetamol and metazimol decreased the consumption of post-operative morphine significantly and suggested that paracetamol should be the first line drug chosen after lumbar disc surgery. The findings of our study seem to conflict with the results of Korkmaz Dilmen et al.[9] However, there are some methodological differences between these two studies: first, we administered the drugs preemptively whereas they started at the end of the operation; second, we used meperidine for PCA, in contrast to morphine PCA. These two drugs have different pharmacokinetics, elimination and active metabolite profile which could result in different findings. A third difference is that the current study was designed in single blinded style for practical reasons, whereas the previous study was conducted in double-blind manner. However, it should be noted that single or double blinding of the studies are not expected to affect the amount of postoperative opioid consumption with PCA devices.

It was shown that inflammation which occurs after laminectomy and discectomy has an important role in post operative pain.[14] Paracetamol is a centrally effective drug which inhibits cyclooxygenase which ensures prostaglandin synthesis selectively. The analgesic and antipyretic effectiveness of paracetamol is similar to acetyl salicylic acid, however it is not effective for inflammation. The reason for the difference in opioid consumption of these two drugs might be the anti-inflammatory characteristics of lornoxicam and the lack of these characteristics in paracetamol. In our study, although there was no statistical difference between Group P and C, we determined that opioid consumption decreased in favor of paracetamol. The small difference with the control group has led us to think that the analgesic effectiveness of paracetamol is weak. Our findings are consistent with the previous work of Toygar et al.,[8] concluding no premptive analgesic effect of intravenous paracetamol in the lumbar disc surgery setting.

On the other hand, Trampitsch et al.[26] introduced the idea that preemptive administration of lornoxicam increases post-operative analgesic quality and a decrease in total analgesic use could be obtained after surgery. The preemptive effect of lornoxicam that was shown in earlier studies ensures the decrease in postoperative opioid consumption in our study.

In a previous study conducted at our institution, it was found that administration of iv paracetamol in addition to morphine administered with iv PCA for post operative analgesia after elective spinal surgery decreased the amount of total morphine consumption by 44% in comparison to iv PCA morphine alone.[27] Delbos et al.[20] determined that morphine consumption decreased by 24% with intravenous paracetamol in their study where they compared daily morphine consumption of paracetamol and placebo. Similarly in our study we determined a decrease in opioid consumption with paracetamol usage in comparison to the control group. The amount

of decrease in postoperative opioid consumption is similar to the study of Delbos et al.,[20] however there are also publications which report greater decreases in the literature.[27,28]

In another study, NSAIDs and paracetamol were compared in terms of effectiveness in dental surgery, it was concluded that NSAIDs ensure better analgesic quality in comparison with paracetamol. [29] The analgesic effects of proparacetamol and ketorolac were found to be similar for total hip arthroplasty.[17] Thus, we think that these different results obtained for analgesic quality may originate from many factors such as the type of surgery, adjuvant drug choice and dosage. As studies in the literature provide different results, we are of the opinion that it would be beneficial to conduct studies in different patient groups in terms of analgesic effectiveness potential with a larger number of patients.

A limitation of the current study is the fact that our study was not double-blinded and the investigators knew the administered drugs of each patient. However, the secondary outcome of the study was mean postoperative opioid consumption and it was directly derived from PCA devices, thus making any bias very unlikely to occur, and it confirms the validity of data presented.

As a result, administration of pre-emptive lornoxicam decreases postoperative NRS scores and the consumption of post-operative opioid for patients undergoing lumbar discectomy surgery. The decrease in opioid requirement is higher with lornoxicam compared to paracetamol. In light of this knowledge, iv lornoxicam administered pre-operatively for lumbar disc hernia surgery ensures a stronger postoperative analgesia, better than iv paracetamol.

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References

1. Ozyilmaz K, Ayoglu H, Okyay RD, Yurtlu S, Koksal B, Hanci V, et al. Postoperative analgesic effects of wound infiltration with tramadol and levobupivacaine in lumbar disk surgeries. J Neurosurg Anesthesiol 2012;24(4):331–5. CrossRef
2. Yazar MA, Inan N, Ceyhan A, Sut E, Dikmen B. Postoperative analgesic efficacy of intravenous dexketoprofen in lumbar disc surgery. J Neurosurg Anesthesiol 2011;23(3):193–7.
3. Tunali Y, Akçil EF, Dilmen OK, Tutuncu AC, Koksal GM, Akbas S, et al. Efficacy of intravenous paracetamol and dexketoprofen on postoperative pain and morphine consumption after a lumbar disk surgery. J Neurosurg Anesthesiol 2013;25(2):143–7. CrossRef
4. Maund E, McDaid C, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. Br J Anaesth 2011;106(3):292-7. CrossRef
5. Carlsson KH, Monzel W, Jurna I. Depression by morphine and the non-opioid analgesic agents, metamizol (dipyrone), lysine acetylsalicylate, and paracetamol, of activity in rat thalamus neurones evoked by electrical stimulation of nociceptive afferents. Pain 1988;32(3):313–26. CrossRef
6. Bannwarth B, Netter P, Lapicque F, Gillet P, Péré P, Boccard E, et al. Plasma and cerebrospinal fluid concentrations of paracetamol after a single intravenous dose of propacetamol. Br J Clin Pharmacol 1992;34(1):79–81. CrossRef
7. Staunstrup H, Ovesen J, Larsen UT, Elbaek K, Larsen U, Krøner K. Efficacy and tolerability of lornoxicam versus tramadol in postoperative pain. J Clin Pharmacol 1999;39(8):834–41. CrossRef
8. Toygar P, Akkaya T, Ozkan D, Ozel O, Uslu E, Gümüş H. Does iv paracetamol have preemptive analgesic effect on lumber disc surgeries?. [Article in Turkish] Agri 2008;20(2):14–9.
9. Korkmaz Dilmen O, Tunali Y, Cakmakkaya OS, Yentur E, Tutuncu AC, Tureci E, et al. Efficacy of intravenous paracetamol, metamizol and lornoxicam on postoperative pain and morphine consumption after lumbar disc surgery. Eur J Anaesthesiol 2010;27(5):428–32. CrossRef
10. Grape S, Tramèr MR. Do we need preemptive analgesia for the treatment of postoperative pain? Best Pract Res Clin Anaesthesiol 2007;21(1):51–63. CrossRef
11. Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth 1995;7(1):89–91. CrossRef
12. Kamaz A, Söğüt Ö, Öksüz H. Comparison of wound infiltration with bupivacaine and levobupivacaine for postoperative analgesia in patients operated for lumbar disc herniation. Anatol J Clin Investig 2008;2(4):141–5.
13. 13.http://dssresearch.com/knowledgecenter/toolkitcalculators/samplesizecalculators.aspx.
14. King JS. Dexamethasone--a helpful adjunct in management after lumbar discectomy. Neurosurgery 1984;14(6):697–700. CrossRef
15. Cashman JN. Non-steroidal anti-inflammatory drugs versus postoperative pain. J R Soc Med 1993;86(8):464–7.
16. Walder AD, Aitkenhead AR. A comparison of droperidol and cyclizine in the prevention of postoperative nausea and vomiting associated with patient-controlled analgesia. Anaesthesia 1995;50(7):654–6. CrossRef
17. Zhou TJ, Tang J, White PF. Propacetamol versus ketorolac for treatment of acute postoperative pain after total hip or knee replacement. Anesth Analg 2001;92(6):1569–75.

18. Ilias W, Jansen M. Pain control after hysterectomy: an observer-blind, randomised trial of lornoxicam versus tramadol. Br J Clin Pract 1996;50(4):197–202.
19. O'Hanlon DM, Thambipillai T, Colbert ST, Keane PW, Given HF. Timing of pre-emptive tenoxicam is important for postoperative analgesia. Can J Anaesth 2001;48(2):162–6.
20. Delbos A, Boccard E. The morphine-sparing effect of propacetamol in orthopedic postoperative pain. J Pain Symptom Manage 1995;10(4):279–86. CrossRef
21. Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. Anesth Analg 1998;86(5):1045–50. CrossRef
22. Işık B, Özköse Z, Gökçe M, Kurt G, Kaymaz M, Yardım Ş. Lomber disk cerrahisinde preemptif uygulanan lornoksikamın analjezik etkinliği. Türk Anest Rean Der Dergisi 2006;34:20–6.
23. Zor ZF, Isik B, Cetiner S. Efficacy of preemptive lornoxicam on postoperative analgesia after surgical removal of mandibular third molars. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117(1):27–31. CrossRef
24. Gillberg LE, Harsten AS, Ståhl LB. Preoperative diclofenac sodium reduces post-laparoscopy pain. Can J Anaesth 1993;40(5 Pt 1):406–8. CrossRef
25. Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. Anesth Analg 1998;86(5):1045–50. CrossRef
26. Trampitsch E, Pipam W, Moertl M, Sadjak A, Dorn C, Sittl R, et al. Preemptive randomized, double-blind study with lornoxicam in gynecological surgery. [Article in German] Schmerz 2003;17(1):4–10. [Abstract] CrossRef
27. Açar A, Özkoçak T, Ayoğlu H, Yurtlu S, Gül Ş, Akay S, ve ark. Spinal cerrahide peroperatif ve postoperatif kullanılan intravenöz parasetamolün postoperatif morfin tüketimine etkisi, Türk Anest Rean Der Dergisi 2008;36:304–9.
28. Hynes D, McCarroll M, Hiesse-Provost O. Analgesic efficacy of parenteral paracetamol (propacetamol) and diclofenac in post-operative orthopaedic pain. Acta Anaesthesiol Scand 2006;50(3):374–81. CrossRef
29. Baygin O, Tuzuner T, Isik B, Kusgoz A, Tanriver M. Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post-operative pain in primary tooth extraction. Int J Paediatr Dent 2011;21(4):306–13.