

## Efficacy of lornoxicam in postoperative analgesia after total knee replacement surgery

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### ÖZET

#### Total diz protezi cerrahisinde postoperatif analjezi amacı ile kullanılan lornoksikamın etkinliği

Total diz protezi operasyonları, postoperatif dönemde ciddi ağrı ile seyretmektedir. Opioidlerin önemli yan etkileri nedeni ile çoklu analjezi yöntemi bu yaşlı hasta grubunda daha uygundur. Lornoksikamın (32mg/48 saat) total morfin tüketimi ve yan etkiler üzerine olan etkisinin araştırıldığı bu çift kör, randomize, plasebo kontrollü çalışmamıza, total diz protezi ameliyatı geçirecek olan yaşlı hastalar dahil edildi. Postoperatif dönemde Grup M (n=23) ve Grup L'ye (n=23) morfin içeren hasta kontrollü analjezi uygulandı. Grup L'ye bu tedaviye ilave olarak 16 mg lornoksikam cerrahiden 15 dk önce, 8 mg lornoksikam da postoperatif 12. ve 24. saatlerde uygulandı. Morfin tüketimi postoperatif 2, 3, 6, 8, 24, 36 ve 48. saatlerde Grup L'de anlamlı olarak düşük bulundu ( $p<0.05$ ). Gruplarda, 48. saatin sonundaki ortalama morfin tüketimi; Grup L'de  $34.60\pm 16.32$  mg iken, Grup M'de  $63.70\pm 15.70$  mg olarak tespit edildi. Eğri altındaki alan değerlendirmesinde (Morfin 0-48 saat) Grup M,  $59\pm 13$  ve Grup L,  $30\pm 13$  olarak değerlendirildi ( $p<0.001$ ). Yan etki insidansı Grup M'de %60 iken, Grup L'de %25 bulundu ( $p<0.05$ ). Grup M'de 8 hastada (%40) bulantı, 3 hastada (%15) kaşıntı görülürken, Grup L'de 3 hastada (%15) bulantı, 1 hastada (%5) kaşıntı, 1 hastada (%5) ağız kuruluğu tespit edildi. Total diz protezi operasyonlarında postoperatif analjezi amacı ile morfine ilave olarak uygulanan lornoksikamın, morfin tüketimi ve yan etki insidansını anlamlı olarak azalttığı görüldü.

**Anahtar kelimeler:** Lornoksikam, postoperatif analjezi, total diz protezi cerrahisi, morfin, hasta kontrollü analjezi

### SUMMARY

In total knee replacement operation, patients have a severe pain in the postoperative period. Because of side effects of opioids, multiple postoperative pain treatment regimens are more suitable in these elderly patients. In this double-blind, randomized, placebo controlled study, the effect of lornoxicam administration (32 mg/48 hour) on morphine consumption and drug-related side effects were investigated in elderly patients undergoing total knee replacement. Group M (n=23) and Group L (n=23) received morphine with patient controlled analgesia (PCA) device postoperatively. Additionally Group L received lornoxicam 16 mg intravenously 15 minutes before surgery and 8 mg at postoperative 12th and 24th hours. Morphine consumption in Group L were significantly lower than in Group M at 2, 3, 6, 8, 24, 36 and 48th postoperative hours ( $p<0.05$ ). At the end of 48th hour mean total morphine consumptions (mean $\pm$ SD) for Group M and Group L were  $63.70\pm 15.70$  mg and  $34.60\pm 16.32$  mg, respectively. AUC (area under the curve) Morphine 0-48h in Group M was  $59\pm 13$  and in Group L it was  $30\pm 13$  ( $p<0.001$ ). Incidence of side effects in Group M were 60% and 25% in Group L ( $p<0.05$ ). In Group M, 8 patients (40%) experienced nausea and 3 (15%) patients experienced itching where as in Group L, 3 patients (15%) experienced nausea, 1 patient (5%) itching, 1 patient (5%) dry mouth. Lornoxicam administration in total knee replacement is associated with decreased morphine consumption for postoperative analgesia and fewer side effects.

**Key words:** Lornoxicam, postoperative analgesia, total knee replacement, morphine, patient controlled analgesia

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## Introduction

Total knee replacement (TKR) may be associated with severe postoperative pain. Osteotomy of the two major bones, the femur and tibia, and the additional reflex spasm of the muscles around the knee causes pain which is additionally aggravated with movement of the knee joint (Bonica 1990). Uncontrolled pain may increase mortality and morbidity due to enhanced metabolic, endocrine and inflammatory responses (Kehlet 1989). Patients undergoing TKR operations are usually in the geriatric age group with restricted cardiac and pulmonary reserves. Postoperative pain management is therefore extremely important but hard to balance in terms of benefits and side effects (Priebe 2000). Opioids are first line drugs for the management of severe pain, but their use is limited since the elderly patients are more susceptible to opioid side effects like excessive sedation, respiratory and cardiovascular depression, nausea/vomiting and gastrointestinal motility problems (Nuutinen et al. 1993, Schug et al. 1991). Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used alone or in combination with opioids for the management of post-operative pain in order to provide better pain relief with fewer side effects.

The pharmacokinetics of lornoxicam do not appear to be significantly altered by advanced age or renal impairment (Bonica 1990). Another advantage of lornoxicam is that it has both oral and intravenous formulations and may be used in various types of chronic, also for acute postoperative pain (Balfour et al. 1996). It is as effective as morphine, pethidine and tramadol in relieving postoperative pain following gynecologic, dental and lumbar disk surgeries with fewer side effects relative to compared drugs (Staunstrup et al. 1999, Rosenow et al. 1998, Ilias and Jansen 1996, Nørholt et al. 1996, Rosenow et al. 1996). In the postoperative setting, lornoxicam has been well tolerated, with a tolerability profile similar to diclofenac (Kidd and Frenzel 1996) but superior to that of indomethacin (Bernstein et al. 1992). To the author knowledge lornoxicam use for postoperative pain management has not been reported previously in major orthopedic surgeries.

The aim of this prospective, double-blinded, randomized, placebo controlled study was to investigate the effect of lornoxicam in reducing the amount of morphine required for postoperative analgesia following TKR surgery. In this setting

side effects of morphine and lornoxicam and total morphine consumptions were also evaluated.

## Material and Method

After obtaining the approval of the ethics committee and written informed consents 46 patients (aged 55-80 years) undergoing TKR surgery were included in the study. Patients with endocrine disorders, severe hepatic and renal diseases, neuropathies, bleeding disorders, preexisting gastric ulcers, gastritis, history of gastrointestinal bleeding, dementia, cooperation disability and sensitivity to lornoxicam or morphine were not included. Cases with operation times longer than 120 minutes were also excluded from the study. All patients were informed about using the Patient Controlled Analgesia (PCA) device during a pre-operative visit the day before the surgery. All patients were premedicated with 2 mg i.v. midazolam (Dormicum®, Roche, Switzerland). Patients were randomized into two groups. Computer assisted randomized treatment assignments were contained in sequentially ordered, sealed envelopes, which were opened just before anesthesia induction. Anesthesia was induced with thiopental sodium 5 mg/kg, fentanyl 1.5 µg/kg and vecuronium 0.1 mg/kg was administered to facilitate endotracheal intubation in both groups. Anesthesia was further maintained with 1-2% Sevoflurane in 50% nitrous oxide/oxygen mixture.

Both groups received 2 mg i.v. morphine 30 minutes before extubation. In the postoperative care unit (PACU), after adequate mental recovery, all patients were informed once more how about to use the PCA device. The PCA device (Pain Management Provider, ABBOTT, USA) was connected to the iv cannula of the patients and set to delivery a 1 mg bolus of morphine with a 15 minute lockout interval in both groups. In addition, Group L received 16 mg 15 minutes before and 8 mg i.v. Lornoxicam (Xefo®, Nycomed, Denmark) 12 and 24 hours after surgery. Group M received saline at the same time and amount of lornoxicam given to patients in Group L. Both lornoxicam and saline syringes were covered with black paper for double blind study design. Time when the patients were able to describe intensity of pain was considered as zero. Heart rate, blood pressure, respiratory rate and morphine consumption of the patients at rest were assessed at 1st, 2nd, 3rd, 4th, 6th, 8th, 12th, 18th, 24th, 36th, 48th postoperative hours by an investigator blind-

**Table 1.** Patient demographics, duration of surgery.

	<b>Group M (n=20)</b>	<b>Group L (n=20)</b>	<b>p Value</b>
Age (yrs) (mean±SD)	64±6	63±4	NS
Gender M/F	3/17	3/17	NS
Height (cm) (mean±SD)	162±8	162±5	NS
Weight (kg) (mean±SD)	77±6	76±5	NS
Duration of surgery (hours)	102±21	98±38	NS
ASA Status (I/II/III)	2/10/8	1/11/8	NS

Values are presented as mean±S.D. and number;  $p>0.05$  vs control group, NS: Not significant

ed to the study protocol. Pain scores were evaluated with a 10 cm Visual Analog Scale (VAS). The patients were assessed for side effects such as nausea, vomiting, itching, dryness of mouth, sweating, urinary retention, sedation, respiratory depression, hypotension, tachycardia, gastric irritation, increased bleeding from the wound, hematemesis and melena. Patients with respiratory rate below 8 per minute, were defined as having respiratory depression and were treated with 0.04 mg i.v. naloxane repeatedly until the desired clinical effect was obtained. Sedation was evaluated by a four point scale; 1: awake, 2: reacting to the verbal stimulant, 3: reacting to the painful stimulant, 4: no reaction to the painful stimulant. Heart rate below 50 per minute was considered as bradycardia and the lowering of mean arterial pressure by 30% compared to pre-operative value was accepted as hypotension. Bradycardia and hypotension were treated with i.v. atropine and ephedrine, respectively. In the event of vomiting or nausea 10 mg iv metoclopramide was given. In the event of pruritus 5 mg iv benzhydramine were administered.

A preliminarily estimated sample size of 15 patients per group with a type 1 error of 0.05 and a type 2 error of 0.20 was based on an expected 30% difference in pain scores at rest, compared with the placebo group. For the statistical analysis of the results, Mann Whitney U test was used for comparison of morphine consumptions of two groups. The patients' characteristics were compared using independent sample t test and chi-square test. Data were expressed as mean ± standard deviation, median and interquartile range, and number of patients. All hemodynamic data was analyzed with ANOVA for repeated measurements and paired Student's t-test with Bonferroni's post hoc test. The incidence of nausea, vomiting, and itching were analyzed with chi-square test or Fisher's exact test when appropriate. The area under the VAS-time curve scores for pain, morphine consumptions, heart rates and

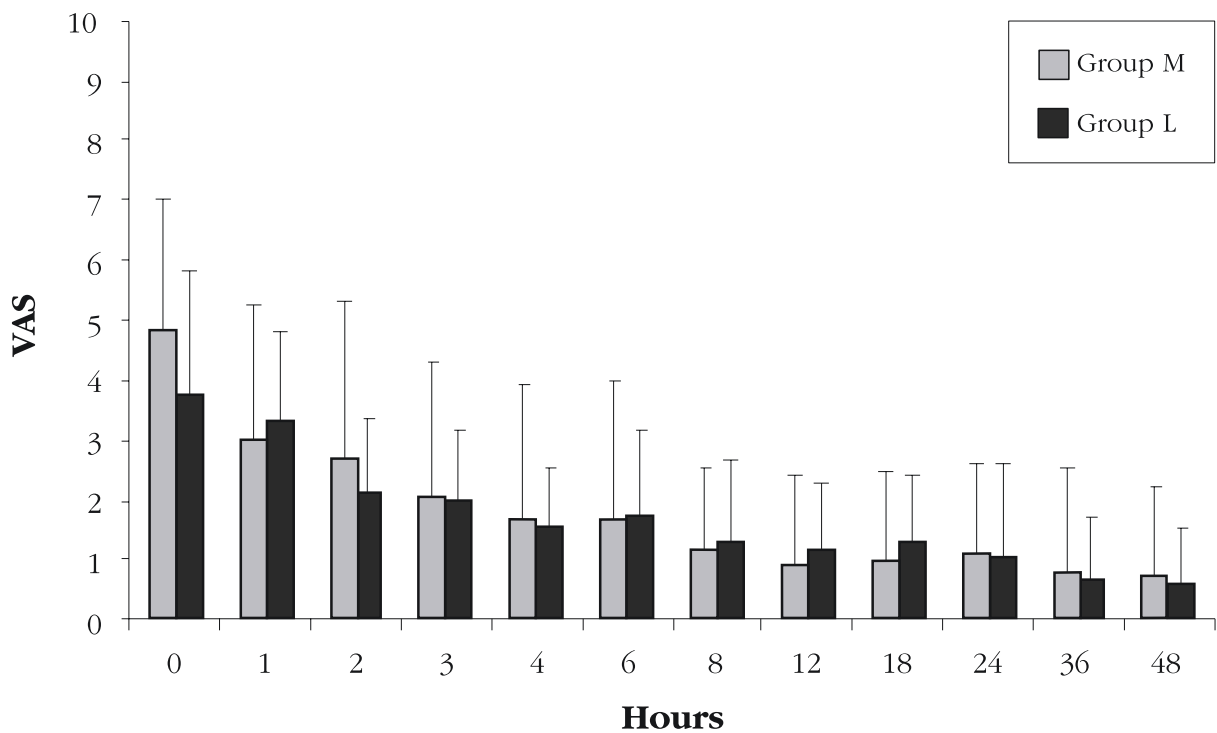
blood pressure during the postoperative period were calculated and further analyzed using independent sample t test. All statistical analyses were computed using SPSS version 10.0 software (SPSS, Chicago, IL, USA). A p value less than 0.05 was considered significant.

## Results

During the course of the study three patients in each group (total 6 patients) were excluded due to inability to cooperate or opioid intolerance. Two patients from Group L could not describe their pain and 2 patients (one from Group M and one from Group L) did not use PCA device although they felt pain. Two patients from Group M were excluded due to opioid intolerance symptoms like anxiety, agitation and excessive sweating. The data of 34 female and 6 male patients were in total 40 patients were included to the study. Demographic data are presented in Table 1. Age, height, weight, gender, ASA status of the patients and duration of surgery in the groups were comparable. Statistical evaluation of mean values of blood pressures, heart rates and respiratory rates of patients at given assessment intervals, revealed no statistical significance ( $p>0.05$ ). Sedation scores in Group M and in Group L during the course of study didn't show statistical significance either ( $p>0.05$ ).

When the patients were fully awake they were questioned for their pain in PACU. First recorded pain scores were  $4.7 \pm 2.2$  and  $3.7 \pm 2.1$  for groups M and Group L, respectively ( $p>0.05$ ). VAS values of the groups were comparable throughout the study (Figure1) ( $p>0.05$ ). Area under the curve (AUC) VAS 0-48 wasn't significant either ( $p>0.05$ ) (Table 2).

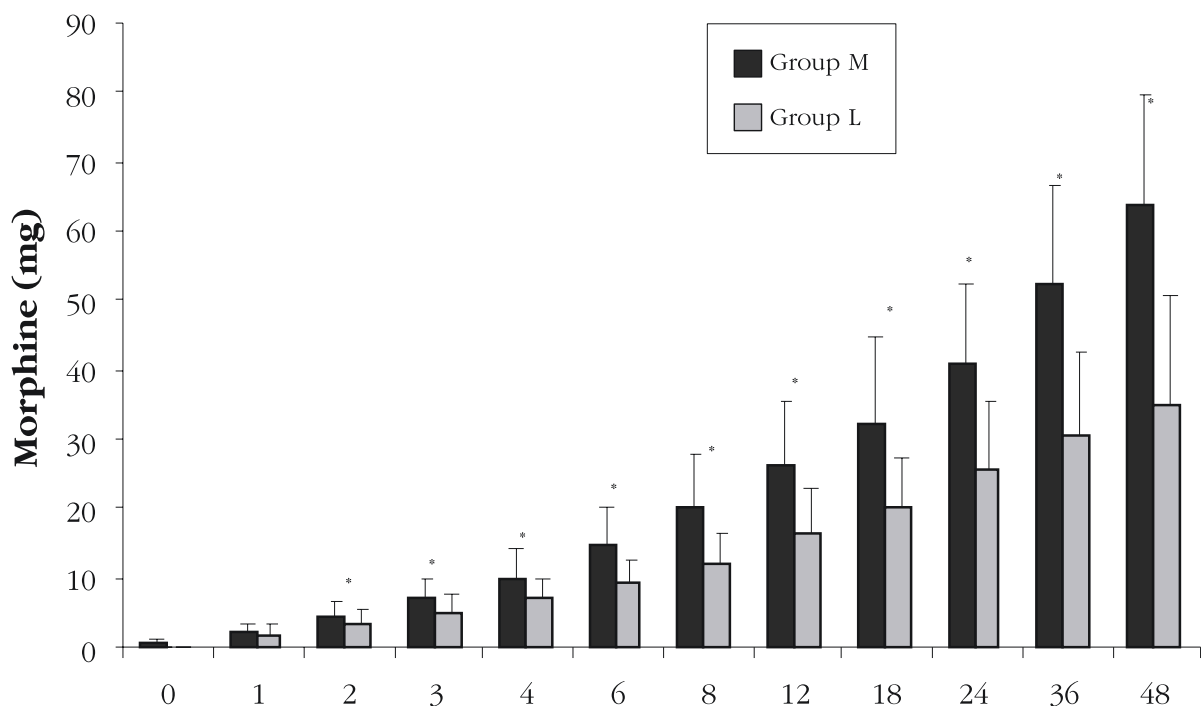
While morphine consumption at given assessment intervals in Group L was significantly lower than Group M at 2, 3, 6, 8, 24, 36 and 48th postoperative hours ( $p<0.05$ ), there wasn't statistical significance between groups in 1, 4, 12, 18th postoper-



**Fig. 1.** VAS, Visual Analogue Scores of the groups. Values are mean±SD.  $p>0.05$  vs Group M.

ative hours (Table 3). Cumulative morphine consumptions were statistically significant except for the first postoperative hour of the study. Mean cumulative morphine consumptions for Group M and Group L were  $63.7 \pm 15.7$  mg's and  $34.6 \pm 16.3$  mg's, respectively at the end of 48th hour ( $p<0.05$ ) (Figure 2). AUC Morphine 0-48 is shown in Table 2 ( $p<0.001$ ). In Group M significantly a higher number of patients (12 vs 5) experienced

side effects than in Group L ( $p<0.05$ ). In Group M, the number of patients who experienced nausea ( $n=9$ ) (45%) was significantly higher than in Group L ( $n=3$ ) (15%), ( $p<0.05$ ). In Group M, 3 patients (15%) experienced pruritus in Group L, one patient (5%) experienced pruritus ( $p>0.05$ ). One patient (5%) in Group L described dry mouth. Patients complaining of pruritus were treated with i.v. benzhydramine.



**Fig. 2.** Cumulative morphine consumptions of the groups. Values are mean ± SD. \*:  $p<0.05$  vs Group M.

**Table 2.** Area under the VAS-time, morphine-time, HR-time, BP-time curve scores during the 48 hours after extubation.

	Group M	Group L	<i>p</i>
AUC VAS	15 (3.15-30.25) 18±17	18.5 (11.0-27.75) 17.7±9.6	0.675
AUC BP	979 (959-1009) 1024 ± 210	1011 (912-1061) 999 ± 87	0.402
AUC HR	898 (875-915) 899 ± 40	906 (874-930) 910 ± 53	0.417
AUC Morphine	58 (45-67) 59 ± 13	28 (17-44) 30 ± 13	0.0001*

Values are presented as median and interquartile range and mean ± SD; \*: *p*<0.001 vs Group M. VAS, Visuel Analogue Scale. BP, Blood Pressure. HR, Heart Rate. AUC, Area Under the Curve.

**Table 3.** Statistical analysis of morphine consumption in both groups.

Follow up times (hour)	Group M morphine (mg)	Group L Morphine (mg)	<i>p</i>
T1	1 (1-3) 1.55±1.23	1 (1-2) 1.65±1.56	0.989
T2	2 (1.25-3) 2.3±1.08	1 (1-2) 1.45±1.05	0.026*
T4	3 (1-4.75) 3±2.45	2 (1-3) 1.9±1.25	0.154
T6	4 (3-5) 4.8±2.74	2 (1-3) 2.25±1.25	0.001*
T8	5 (3.25-7.5) 5.3±3.0	2 (1.25-4) 2.8±1.76	0.005*
T12	5.5 (2.0-8.0) 5.8±4.2	4 (2-6) 4.35±3.13	0.315
T18	5.5 (3.0-6.75) 6.15±4.85	4 (2.25-5) 3.8±1.76	0.073
T24	7.5 (4-13) 8.55±5.18	4.5 (2-8.5) 5.4±4.3	0.040*
T36	10 (6-22) 12.8±8.8	2.5 (2-7) 4.59±4.51	0.002*
T48	8 (4.25-15.75) 10.4±8.63	1.5 (0-7.75) 4.59±6.41	0.011*

Values are presented as median and interquartile range and mean±SD; \*: *p*<0.05 vs Group M.

## Discussion

Multimodal analgesia protocols may increase analgesic efficacy. Severe postoperative pain may be treated with different combinations of drugs or techniques, namely peripheral nerve blocks, epidural local anesthetics and/or opioids, intravenous opioids or NSAID's via PCA (Vendittoli et al. 2006, Rosaeg et al. 2001). In this study intravenous administration of morphine by PCA was combined with intermittent administration of

lornoxycam. Lornoxicam administered preoperatively and at postoperative 12th and 24th hours significantly reduced intravenous morphine consumption in elderly patients undergoing TKR surgery. It was also found that side effects were significantly reduced compared to the control group in which i.v. morphine PCA was used alone.

Lornoxicam is a NSAID of the oxicam group. It acts by inhibiting synthesis of prostaglandins and

its pain promoting derivatives via inhibiting the cyclo-oxygenase enzyme in the arachidonic acid pathway. As with other oxycam NSAIDs, lornoxicam is highly bound (90%) to plasma proteins with a low apparent volume of distribution (0.2 L/kg). However, it readily penetrates into perivascular interstitial spaces, including synovial fluid (Balfour et al. 1996). Lornoxicam has potent anti-inflammatory and analgesic effects like other oxycams but unlike other oxycams it has a shorter half life (3-5 hours), which decreases the incidence of side effects due to long plasma half life (Radhofer-Welte and Rabasseda 2000, Olkkola et al. 1994). In comparative studies, lornoxicam was as effective as parecoxib, and more effective than ketoprofen in the early postoperative period. (Karaman et al. 2006, Papadima et al. 2006) In the present study lornoxicam was significantly more effective in pain relief than placebo in the early postoperative period also.

Opioids are commonly used agents given by a number of different routes for postoperative pain but their side effects limit their use and analgesic efficacy (Schug et al. 1991). In this study, two patients in the morphine group developed morphine intolerance and were excluded from the study. Other postoperative pain management methods were applied for these patients. NSAIDs are both efficacious and generally well tolerated and therefore provide a useful alternative to opioid analgesics for short-term use (Nuutinen et al. 1993). Their analgesic effect was shown to be comparable with morphine, tramadol, and meperidine in many studies (Staunstrup et al. 1999, Rosenow et al. 1998, Ilias and Jansen 1996, Nørholt et al. 1996, Rosenow et al. 1996). To the authors knowledge there is no clinical study investigating the analgesic effect of lornoxicam in patients undergoing TKR. Therefore direct comparison of lornoxicam dose requirement in this type of surgery was not possible. In a study by Rosenow et al (1998) mean lornoxicam consumption was 19,8 mg administered by intravenous PCA in patients undergoing discectomy without spinal instrumentation. Type of surgical intervention effects analgesic requirement (Yorukoglu et al. 2005). TKR is a type of surgery which causes severe pain. So in this study in addition to bolus intravenous administration of lornoxicam, i.v. morphine PCA was also used and provided sufficient analgesia.

In the literature, lornoxicam was better tolerated than morphine, as evidenced by the lower overall incidence of adverse events (Rosenow et al. 1998,

Nørholt et al. 1996). In recent study lornoxicam used in combination with morphine significantly reduced morphine related side effects. In addition we didn't observe severe side effects with lornoxicam.

Patients in the geriatric age group with multiorgan system malfunctions may be prone to adverse events in the postoperative; however, the need for sufficient pain relief can not be overlooked. Pharmacokinetic studies of lornoxicam were performed in elderly volunteers; (aged 66-79) results did not indicate any accumulation after multiple dose of lornoxicam in these patients (Radhofer-Welte and Rabasseda 2000). Enhanced enterohepatic elimination of lornoxicam may compensate for reduced renal elimination in those with severe renal dysfunction; however accumulation of the inactive major metabolite occurred in patients with impaired hepatic function (Balfour et al. 1996). In this study a total dose of 32 mg lornoxicam was used. Use of this total amount of lornoxicam was found to be safe in a previous study (Rosenow et al. 1998).

In studies comparing the effective analgesic dose of lornoxicam, 4 mg of lornoxicam was found superior to placebo but not as effective as 8-32 mg lornoxicam in postoperative pain treatment. Lornoxicam doses equal to or greater than 8 mg's are essential for postoperative pain relief (Nørholt et al. 1995). In present study, the total 24 mg of i.v. lornoxicam used for the first 24 hours and 8 mg for the second 24 hours decreased the total amount of morphine consumed by 46% in Group L compared to Group M at the end of the study (63.7 vs 34.6 mg). This decrease was attributed to the additional analgesic effect of lornoxicam. In a colorectal distention model of acute visceral pain in rats, lornoxicam was less active than morphine as an analgesic. However, the addition of lornoxicam to morphine increased the effect of the latter and allowed lower doses of morphine to be used, which may be useful in the prevention of opiate adverse reaction (Towart et al. 1998). For this purpose we used lornoxicam with morphine utilizing to increase analgesic efficacy and decrease opioid related side effects.

In a study by Rosenow et al. (1998), two groups of patients undergoing lumbar disk surgery, lornoxicam and morphine were used with PCA device setting. At the end of 24 hours total doses of lornoxicam and morphine consumption were 19.8 mg and 22.2 mg, respectively. The incidence of side effects was 25% and 60% for lornoxicam

and morphine, respectively. Lornoxicam provided statistically equal analgesia to morphine. The onset of analgesia was slightly faster with morphine. The demand for PCA lornoxicam was greater than for morphine at the beginning of the treatment, but in the second 12-h period the demand for morphine was higher. There was a trend for the onset of analgesia with lornoxicam to be slower than that with morphine. This difference in onset of pain relief may partly account for the slightly higher rate of premature termination of the study in the lornoxicam group due to non response (28.3% vs 18.0% with morphine) (Rosenow et al. 1998).

In the present study a lornoxicam and morphine combination was better tolerated than morphine alone. Addition of lornoxicam provided decreased consumption of morphine which resulted in a decreased frequency of side effects. None of the patients in the lornoxicam group discontinued the study while two patients in morphine group were excluded due to morphine intolerance.

Statistical insignificance of mean morphine consumption of the groups in the first postoperative hour was attributed to the delayed analgesic effect of lornoxicam. Similar results were shown in study of Karaman S et al. (2006), lornoxicam was administered in preoperative period and it decreased morphine usage after second postoperative hour. In previous studies evaluating the analgesic efficacy of lornoxicam for postoperative analgesia management, the follow up duration was 24 hours in the postoperative period; therefore data concerning analgesic consumption on the second postoperative day remained obscure (Rosenow et al. 1996, Rosenow et al. 1998) In this study in Group M, total morphine consumption for the first 24 hours was 40.5 mg and 23.2 mg for the next 24 hrs (24-48 hr). The decrease in morphine consumption was 43%. In Group L, the amount of morphine consumed were 25.5 and 9.1 mg for the first and second 24 hours, respectively and the decrease was about 64%. In this group, only 8 mg lornoxicam was used in the second postoperative day. Findings in some previous studies revealed that endogenous opioid release might also contribute to the analgesic effects of lornoxicam. Patients suffering from acute low back pain were treated with iv lornoxicam during 5 days in a study of Kullich and Klein (1992). Repeated doses of lornoxicam resulted in increased plasma levels of dynorphin and beta-

endorphin; this finding was used to explain the increased analgesic efficacy of the drug. In this study although lornoxicam was administered at a much lower dose on the second postoperative day, morphine consumption decreased considerably (64%). This may be attributed to the prolonged effect of the total dose of lornoxicam administered on the first postoperative day or a cumulative effect of lornoxicam administered on a scheduled basis. In the study of Norholt et al. (1996) the median duration of analgesia achieved with 20 mg of morphine (8,2 h) was slightly longer than that of 8, 16 or 20 mg of lornoxicam (5.1, 7.0 and 6.8 hrs, respectively) and more than double that of 10 mg of morphine (2.5 h). The reason for this issue remains to be discussed in future studies.

In conclusion 24 mg of lornoxicam for the first and 8 mg of lornoxicam used for the second 24 hour reduced morphine consumption and side effects related to morphine consumption without additional side effects of lornoxicam used in patients undergoing TKR. Addition of lornoxicam also reduced the incidence of nausea from 40% to 15%, and the incidence of itching from 15% to 5% during postoperative pain control provided by morphine. Furthermore, the lornoxicam and morphine combination possesses a more favourable tolerability profile than morphine and thus also represents an attractive alternative for the treatment of severe acute pain.

## Acknowledgements

We would like to thank Professor Y. Ates for guidance in the preparation of this manuscript and Z. Alanoglu, MD for his help.

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