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ORIGINAL ARTICLE

Comparison of lornoxicam and low-dose tramadol for management of post-thyroidectomy pain

Tiroidektomi sonrası ağrı kontrolünde lornoksikamın düşük doz tramadol ile karşılaştırılması

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Summary

Objectives: The present study sought to compare the analgesic efficacy and adverse effects of intravenous (IV) lornoxicam and tramadol to investigate if lornoxicam is a reasonable alternative to a weak opioid for post-thyroidectomy pain.

Methods: Fifty patients of American Society of Anesthesiologists class I or II, 18 to 65 years of age, and who underwent thyroidectomy were assigned to 2 groups in a randomized manner. Group L received 8 mg of lornoxicam IV and Group T received 1 mg/kg of tramadol IV at conclusion of the operation. Pain intensity of patients was recorded at 15 and 30 minutes, and at 1, 2, 3, 4, 6, 12, and 24 hours after the initial dose with Numerical Rating Scale (NRS) and Ramsey Sedation Scale. Electrocardiogram, heart rate, systolic/diastolic and average artery pressure and peripheral oxygen saturations were monitored continuously during this period. Patients completed satisfaction questionnaires at 24th hour.

Results: Both drugs produced acceptable analgesia; however, significantly fewer patients reported 1 or more adverse events with lornoxicam than with tramadol. Most commonly seen in Group T was nausea/vomiting. NRS scores at 15 minutes, 30 minutes, and 1 hour were lower in Group L than in Group T ($p<0.05$), but there was no significant difference between groups after postoperative first hour. First analgesic requirement time was significantly longer in Group L compared to Group T ($p<0.001$). No serious complications were seen in either group.

Conclusion: Lornoxicam is a safe and effective analgesic that may be used with fewer complications than low-dose tramadol for treatment of moderate to severe postoperative pain.

Keywords: Lornoxicam; postoperative pain; thyroidectomy; tramadol.

Özet

Amaç: Bu çalışmada intravenöz lornoksikam ve tramadolun analjezik ve yan etkilerini karşılaştırdık. Amacımız lornoksikamın tiroidektomi sonrası ağrı kontrolünde opioidlere alternatif olarak kullanılabilirliğini araştırmaktır.

Gereç ve Yöntem: ASA I ve II olan 18–65 yaş arası 50 hasta tiroidektomi sonrası randomize bir şekilde iki gruba ayrıldı. Grup L 8 mg IV lornoksikam ve Grup T 1 mg/kg IV tramadol aldı. Ağrı yoğunluğu 15 ve 30. dakika, 1, 2, 3, 4, 6, 12, 24. saatlerde Sayısal Derecelendirme ve Ramsey Sedasyon Ölçekleri sayesinde değerlendirildi. Hastalar monitörize edilerek elektrokardiyogram, kalp hızı, sistolik/diyastolik kan basıncı ve ortalama kan basıncı, periferal oksijen saturasyonu değerleri takip edildi. Hasta memnuniyet anketi 24. saatte yapıldı.

Bulgular: Her iki ilaç yeterli analjeziyi sağlamakla birlikte sadece birkaç hastada bulantı/kusma gibi yan etkiler gelişti. 15 ve 30. dakika ile 1. saat NRS skorları Grup L de daha düşük iken ($p<0.05$), 1. saatten sonra bakılan ölçeklendirmelerde iki grup arasında anlamlı farklılık saptanmamıştır. İlk analjezik gerekme zamanı Grup L de daha uzundu. ($p<0.001$). Hiçbir hastada önemli bir komplikasyon gelişmedi.

Sonuç: Intravenöz lornoksikam, tramadola göre orta-ağır ağrı yönetiminde kullanışlı bir alternative olarak görünmektedir.

Anahtar sözcükler: Lornoksikam; postoperatif ağrı; tiroidektomi; tramadol.

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Introduction

The International Association for the Study of Pain (IASP) defines pain as "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain is an emotional experience including psychogenic components, and always subjective. Therefore, pain varies from one person to another and even in same person within different times.[1]

Pain is one of the main postoperative adverse outcomes causing distress to patients, prolonging hospital stay, and increasing surgical morbidity and mortality. Acute postoperative pain thresholds and pain tolerance may differ among patients. Thus, no standard analgesic drug or dose is available for patients.[2] Since the cause of pain varies depending on the patient and type of the surgery, treatment of acute postoperative pain is variable.[3,4] At the present time, many alternative drugs with various active ingredients are used for postoperative pain control. Opioids have demonstrated efficacy, and often are drugs of choice, in the management of postoperative pain. However, their use is often limited by adverse drug events, and alternative drugs with fewer adverse effects have been widely studied.

Tramadol, a synthetic analogue of codeine, is a centrally acting atypical opioid analgesic with a unique active metabolite, M1 (O-desmethyltramadol). It is an atypical opioid due to being a serotonin-norepinephrine reuptake inhibitor and a selective agonist of μ receptors. In therapeutic dosage, tramadol-induced respiratory depression is extremely rare.[5] Lornoxicam is a non-steroid anti-inflammatory drug (NSAID) of the oxicam class. Like other NSAIDs, anti-inflammatory and analgesic activity of lornoxicam is related to its' inhibitory action on prostaglandin and thromboxane synthesis. It is a useful agent in perioperative pain, with a rapid onset of analgesic effect and minimal and short-term effects on thrombocyte aggregation due to its short half-life. Therefore, postoperative pain is the best indication for lornoxicam.[6,7]

The aim of this study was to compare the efficacy and side effects of lornoxicam vs tramadol in patients with post-thyroidectomy pain.

Methods

All patients were referred for their elective thyroidectomy operations for benign thyroid lesions between September 2012 and April 2013. Written informed consent from the patients was taken by researchers. The study was approved by the Local Ethics Committee. Fifty healthy ASA physical status I or II patients, aged 18–65 years, who were scheduled to undergo total thyroidectomy, were enrolled in this study. Patients were not selected in any way other than being the first or second patient on the morning operating list in order to provide the maximum time of close observation in the recovery ward. In this double-blind, randomized study, the patients were randomly separated into two groups to receive lornoxicam (n=25) or tramadol (n=25) by an anesthesiologist, postoperatively. The surgeons, anesthesiologists, and recovery room staff members were all blinded with regard to study medications.

Exclusion criteria's were:

- The patients who have classified ASA III and IV and patients with a history of NSAID sensitivity,
- Congestive heart failure, coagulation deficiency, renal failure,
- Gastrointestinal system diseases (history of gastritis, peptic ulcer, esophageal varices in the last 6 months),
- Asthma, alcohol addiction, convulsion anamnesis
- Patients with an operation time longer than two hours
- The ones with opioid addiction

All patients' laboratory tests, physical examinations and vital signs were evaluated. Patients with body mass index under 30 kg/m^2 were included to the study. All patients were monitored for electrocardiogram, heart rate, systolic/diastolic and average blood pressure and peripheral oxygen saturation during and after surgery. Before administration of study drugs, no premedication that may affect analgesia was used.

The patients were divided into two groups according to the drug that was used; Group T (n=25) and Group L (n=25). Group T received 1 mg/kg tramadol i.v. (Tramadol, Sandoz®) (n=25) and Group L received 8 mg. lornoxicam i.v. (Xefo, Abdi İbrahim®) (n=25). After preoxygenation for 3 minutes with 100% oxygen,

Table 1. Patients demographics and anesthetic procedure

Patient characteristics	Tramadol group (n=25)		Lornoxicam group (n=25)	
	Mean	Min.-Max	Mean	Min.-Max
Age (years)	35	18–65	32	22–65
Body mass index (kg/m^2)	22	19–28	23	19–26
Supplemental fentanyl (mcg)	65	50–85	62	50–80
Duration of surgery (min)	114	74–154	128	88–160

Min: Minimum; Max: Maximum. Data are presented as mean and range (min-max).

anesthesia was induced with 2–2.5 mg/kg propofol (Propofol, Fresenius®), 1 mcg/kg fentanyl (Fentanyl, Janssen-Cilag®) for all patients. Vecuronium bromide (Norcuron, Organon®) 0.1 mg/kg was given to facilitate endotracheal intubation. Following endotracheal intubation, 1–1.5% sevoflurane (Sevorane, Abbott®) in 50% O_2-N_2O mixture was used for maintenance of anaesthesia. Post-operative analgesia was initiated immediately after the wound closure by surgeons with tramadol 1 mg/kg or lornoxicam 8 mg administered i.v. in a bolus form. Sevoflurane concentration was reduced to 0.5% after analgesic medication. Anesthetic gases were turned off at the end of the surgery and the patients were oxygenated with 6 L/min oxygen. When spontaneous breathing returned, 0.01 mg/kg atropine and 0.03 mg/kg neostigmine were given to reverse the neuromuscular block. The time that patients were in awaken state following extubation was recorded for determination of initial analgesic period.

For rescue analgesia, patients could receive diclofenac sodium 75 mg intramuscular on request for patients suffering from postoperative pain (NRS>4), and the time that passed for initial analgesic requirement was recorded for each patient. No other analgesic was permitted during the first week after surgery. We also monitored the fentanyl consumption during anesthesia. Demographical characteristics of patients (gender, age, weight), anesthesia and operation periods, postoperative Numerical Rating Scale (NRS) scores (0=no pain, around 5=moderate pain, 10=worst pain imaginable), systolic/diastolic and average artery pressures, heart rate, peripheral oxygen saturation, respiration rate, Ramsey sedation scale (RSS) scores at 15, 30 min. and 1, 2, 3, 6, 12 and 24 h were recorded (Table 1 and 2). The patient satisfaction questionnaires were evaluated at 24 h (1: very bad, 2: bad, 3: good, 4: very good, 5: perfect). Postoperative nausea and vomiting were also followed up (0: none, 1: mild, 2: mean, 3: severe).

Table 2. Ramsey Sedation Scale

Sedation score	Response
1	Anxious or restless or both
2	Cooperative, orientated and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

Side effects of the drugs and complications were also recorded (allergic reactions, hypotension, nausea and vomiting, respiratory depression). Patients suffering severe nausea and vomiting were treated with intravenous 10 mg metoclopramide. Respiration rates less than 8 breaths per minute were defined as respiratory depression and treatment with 0.04 mg naloxone was planned if it ever occurs. Heart rate less than 50 beats per minute was defined as bradycardia and treatment with intravenous atropine was planned for correction. If postoperative average artery pressure was 30% less than preoperative average artery pressure, it was accepted as hypotension and treated with intravenous 0.9% NaCl and ephedrine. Patients that suffered itching were treated with intravenous 5 mg pheniramine.

Statistical analysis

Statistical analysis was performed with Graphpad Prisma® package program (version 3.0). For the assessment of the data; matched one-way variance analysis for repeated measures of multiple groups, Newman Keuls multiple comparison test for subgroup analysis, independent t test for the compari-

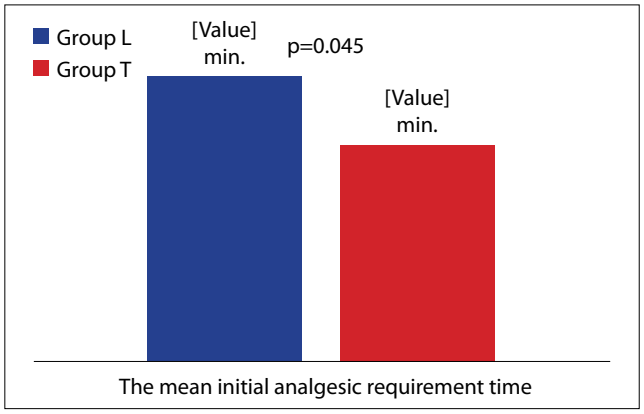


Figure 1. The mean initial analgesic requirement time.

son of double groups and chi-square test for the comparison of qualitative data were used, in addition to definitive statistical methods (average, standard deviation). P<0.05 was considered as significant.

Results

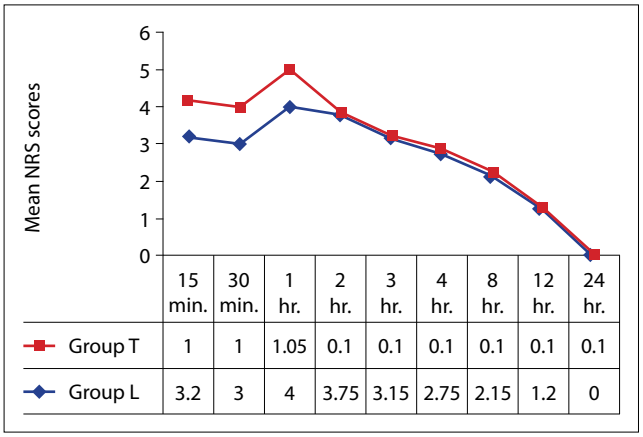
A total of 55 patients entered the study, and 50 (25 in group L and 25 in group T) of them were eligible for the study. Three patients in the lornoxicam group and 2 patients in the tramadol group were withdrawn due to allergic reactions. Patient's characteristics before tramadol or lornoxicam were shown in Table 1.

There was no significant difference between the groups regarding to age, height, body weight, and body mass index (p>0.05). Also no difference was found for ASA status, the duration of anesthesia and surgery between both groups (p>0.05).

The initial analgesic requirement time of lornoxicam group is found to be significantly longer than tramadol group (p=0.045) (98.36±45.21 min. for lornoxicam and 74.86±34.58 min. for tramadol) (Figure 1).

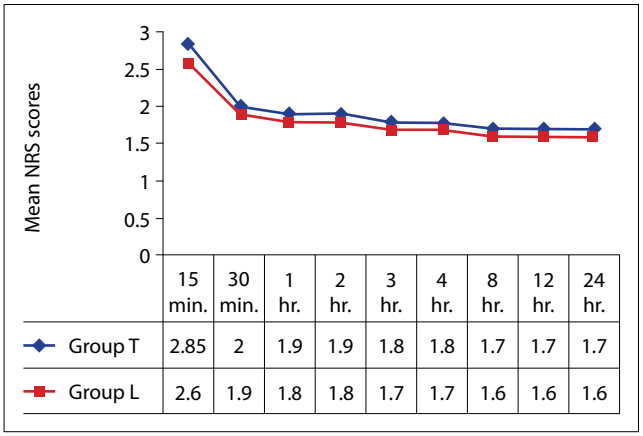
NRS scores at 15 min, 30 min, and 1 h were lower in Group L than in Group T (p=0.022). There was no significant difference between groups after postoperative first hour (Figure 2). Additional IM diclofenac was required for 4 patients in lornoxicam group and 7 patients in tramadol group.

RSS scores of lornoxicam and tramadol groups at 15 min, 30 min, 1h, 2h, 3h, 4h, 8h, 12h, 24h were not significantly different (p>0.05) (Figure 3). However, a statistically significant difference was observed in-group RSS scores as time goes by, for both groups (p=0.0001).



	15 min.	30 min.	1 hr.	2 hr.	3 hr.	4 hr.	8 hr.	12 hr.	24 hr.
Group T	1	1	1.05	0.1	0.1	0.1	0.1	0.1	0.1
Group L	3.2	3	4	3.75	3.15	2.75	2.15	1.2	0

Figure 2. Mean NRS scores of the groups (p=0.022).



	15 min.	30 min.	1 hr.	2 hr.	3 hr.	4 hr.	8 hr.	12 hr.	24 hr.
Group T	2.85	2	1.9	1.9	1.8	1.8	1.7	1.7	1.7
Group L	2.6	1.9	1.8	1.8	1.7	1.7	1.6	1.6	1.6

Figure 3. Mean RSS scores of the groups (p>0.05).

No statistically significant difference was observed for systolic/diastolic and average artery pressure, heart rate and average respiratory rate between lornoxicam and tramadol groups at 15 min, 30 min, 1h, 2h, 3h, 4h, 8h, 12h, 24h (p>0.05).

One patient experienced itching in Group L, whereas five other patients presented nausea and vomiting, one in Group L and four in Group T. The patients reported no remarkable complications, and patient satisfaction scores were not significantly different between groups (p>0.05).

Discussion

Postoperative pain is a commonly seen subgroup of acute pain, and is a complex response to tissue trauma during surgery. Nociception involves the 4 processes of transduction, transmission, perception, and modulation. These processes are highly complex, but a simple summary can aid understanding of pain mechanisms and pain interventions. First, tissue damage releases chemical mediators, such as

prostaglandins, bradykinin, serotonin, substance P, and histamine. These substances then activate nociceptors, resulting in transduction, or the generation of an action potential (an electrical impulse). In the second process, transmission, the action potential moves from the site of injury along afferent nerve fibers to nociceptors at the spinal cord. Release of substance P and other neurotransmitters carry the action potential across the cleft to the dorsal horn of the spinal cord, from where it ascends the spinothalamic tract to the thalamus and the midbrain. Finally, from the thalamus, fibers send the nociceptive message to the somatosensory cortex, parietal lobe, frontal lobe, and the limbic system, where the third nociceptive process, perception, occurs.[8]

Opioids are unique in that they not only block the incoming nociceptive signals to the brain but also act at higher brain centers, controlling the affective components of the pain. Non-opioid analgesics have principally analgesic, antipyretic, and anti-inflammatory actions. The mechanism of action of NSAIDs involve blockade of the production of prostaglandins by inhibition of the enzyme cyclooxygenase (COX) at the site of injury in the periphery, thus decreasing the formation pain mediators in the peripheral nervous system. Tissue damage following the surgery is repaired with wound healing process, and during this damage and healing process, several mediators that trigger the pain are released. Drugs show their analgesic effects by altering different mechanism in this pathway in various levels.

In their placebo-controlled study, Arslan et al.[9] found that lornoxicam decreased the weak opioid need, the incidence of nausea and vomiting and postoperative pain scores postoperatively. Moreover, first analgesic requirement time was significantly longer in lornoxicam group when compared to placebo group (101.7 vs 37.9 min, $p<0.001$). Similarly, Işık et al.[10] reported that preoperative 8 mg lornoxicam was more effective than 1 mg/kg tramadol for controlling early postoperative tonsillectomy pain in adult patients, with similar side effects. Verbal Pain Scale (VRS) pain scores at 30 min. and 60 min. in tramadol group were higher than lornoxicam group ($p=0.049$, $p=0.007$). Furthermore, the number of patients requiring rescue analgesics during the first 6 hours in lornoxicam group was lower than tramadol group, similar to our study. In literature, half-lives of tramadol and lornoxicam are reported to be 5–6 hours and 3–5 hours, respectively. In our study, the average time to first analgesic requirement in both groups were found to be closer to drugs' half-lives.

Mentes et al.[11] reported no significant difference between the analgesic effects of lornoxicam and tramadol after inguinal hernia repair with respect to VAS score. However, in our study NRS scores at 15 min, 30 min and 1 hour in lornoxicam group were lower than tramadol group. When these results are evaluated together, it can be suggested that even though the analgesic effect of lornoxicam has a rapid onset, tramadol is more potent in late postoperative period and has a longer duration of analgesic action. In their study, the pain scores were found to be higher and first analgesic requirement time was shorter in all groups, compared to our study. The reason for this difference may be due to shorter duration of surgery in our study. The findings in the literature also showed us that the administration of analgesic drugs during the last phases of surgery, just before the surgery ends, might facilitate to get pain under-control.[12,13]

Ganidagli et al.[14] compared IM tramadol to IM pethidine in 50 patients following abdominal operations. At 60, 90 and 120 minutes, sedation scores in pethidine group were higher than tramadol group. Also, peripheral oxygen saturation in pethidine group was significantly lower than tramadol group at 60 and 120 minutes, which makes tramadol the weak opioid drug of choice for postoperative pain, with lower side effect potential.

İnan et al.[15] compared lornoxicam with morphine for postoperative analgesia in 46 patients following total knee replacement surgery. They could not find a significant difference between postoperative hemodynamic scores of patients ($p>0.05$). However, incidence of side effects was 60% in morphine group and 25% in lornoxicam group ($p<0.05$). Staunstrup et al.[16] investigated the efficacy and tolerability of lornoxicam versus tramadol in postoperative pain. In their study, patients received a single dose of lornoxicam 16 mg and tramadol 100 mg. Moreover, they proposed intramuscular lornoxicam offers a

useful alternative to tramadol for the treatment of moderate to severe postoperative pain. Similarly, our findings suggest that lornoxicam is a safe and efficient drug for post-thyroidectomy pain when compared to tramadol.

In our study, no significant difference was found between the groups in terms of the level of sedation in postoperative period and peripheral oxygen saturations. The heart rates and blood pressure values of the patients who were suffering from pain in postoperative period were increased in parallel to postoperative pain. Highest values were determined just before the first analgesic requirement time. No hypotension and bradycardia was observed in any patient in Group T, itching, which did not require any intervention, was observed only in 3 patients (12%).

Nausea and vomiting are two of the most frequently seen side effects of tramadol. However, in our study, only the first hour nausea and vomiting rates in lornoxicam group were found to be lower than tramadol group. Previous studies also have shown no significant difference between lornoxicam and tramadol in terms of nausea and vomiting.[11]

It is a known fact that NSAIDs inhibit platelet aggregation and prolong bleeding time; hence they can cause postoperative bleeding. However, the studies showed that lornoxicam does not increase the risk of bleeding in therapeutic dosage.[16–18] Krishna et al. reported[19] no significant increase in post-tonsillectomy bleeding after NSAID administration. In our study, none of the patients had postoperative bleeding in any group. Also, patient satisfaction was not significantly different for lornoxicam and tramadol groups (p=0.532).

Conclusion

As a result of this study, it can be stated that even though the analgesic effect of lornoxicam has a rapid onset, tramadol is more potent in late postoperative period and has a longer duration of analgesic action. Moreover, tramadol has more side effects than lornoxicam.

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