EFFICACY OF DEXKETOPROFEN TROMETAMOL FOR ACUTE POSTOPERATIVE PAIN RELIEF AFTER ENT SURGERY: A COMPARISON WITH PARACETAMOL AND METAMIZOLE

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ABSTRACT

• ***Objective:*** *In this prospective, double-blind, randomized study we compared the efficacy of three i.v. non-opioid analgesics for postoperative pain relief after ear, nose and throat (ENT) surgery.*

• ***Material and Method:*** *Ninety patients, aged between 18-65 years and undergoing elective ENT surgery were enrolled into the study protocol that was carried out in Tepecik Education and Research Hospital, Izmir, Turkey between February and May 2009. General anesthesia protocol was the same in all patients. At the end of surgery, the patients were randomly assigned into 3 groups (n=30 in each group). Group D received 50 mg dexketoprofen trometamol (three times daily), Group P received 1 gr paracetamol (four times daily) and Group M received 1 gr metamizole (three times daily) intravenously. We evaluated the level of postoperative pain (by visual analoque scale and verbal rating scale at 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 12 h, and 24 hours after surgery) and sedation scores. Intramuscular pethidine 1 mg/kg was administered to patients requiring additional analgesia, and treatment-related adverse effects (nausea, vomiting, dyspepsia, skin rash, headache) were noted.*

• ***Results:*** *The pain scores were significantly lower in the dexketoprofen trometamol group compared with the other groups ($p<0.05$). Pethidine requirement was found to be significantly higher in the Groups P and M ($p<0.05$). No significant difference was observed in sedation scores and adverse effects among the groups ($p>0.05$).*

• ***Conclusion:*** *Efficacy of dexketoprofen trometamol in the management of acute postoperative pain was superior to that of other non-opioid analgesics used in this study.*

• ***Key Words:*** *Dexketoprofen trometamol, paracetamol, metamizole, postoperative analgesia, ENT surgery.* ***Nobel Med 2010; 6(2): 47-52***

ÖZET

KBB CERRAHİSİNDE AKUT POSTOPERATİF ANALJEZİDE DEKSKETOPROFEN TROMETAMOLUN ETKİNLİĞİ: PARASETAMOL VE METAMİZOL İLE KARŞILAŞTIRILMASI

• **Amaç:** Prospektif, çift-kör, randomize çalışmamızda kulak burun boğaz cerrahisinde (KBB) postoperatif analjezide, üç intravenöz nonopioid analjeziğin etkinliğini karşılaştırdık.

• **Materyal ve Metod:** İzmir Tepecik Eğitim ve Araştırma Hastanesi'nde Şubat-Mayıs 2009 tarihleri arasında, yaşları 18-65 olan elektif KBB cerrahisi uygulanan 90 hasta çalışmaya dahil edildi. Bütün hastalara standart genel anestezi uygulandı. Cerrahi sonunda hastalar randomize olarak üç gruba ayrıldı (her bir grup için n=30). Grup D'ye 50 mg deksketoprofen trometamol (günde üç kez), Grup P'ye 1 gr parasetamol (günde dört kez) ve Grup M'ye 1 gr metamizol (günde üç kez) intravenöz olarak uygulandı. Postoperatif ağrı düzeyi (görsel analog skala ve sözel analog skala ile cerrahi sonrası 1, 2, 3, 4, 5, 6, 12 ve 24. saatlerde) ve sedasyon skorları değerlendirildi. Ek analjezi gereksiniminde intramuskuler pethidin 1 mg/kg uygulandı ve tedaviye bağlı yan etkiler (bulantı, kusma, dispepsi, cilt kızarıklığı, baş ağrısı) kaydedildi.

• **Bulgular:** Ağrı skorları, deksketoprofen trometamol grubunda diğer gruplarla karşılaştırıldığında belirgin olarak düşük bulundu (p< 0,05). Pethidin gereksinimi Grup P and Grup M'de belirgin olarak yüksek bulundu (p< 0,05). Gruplar arasında sedasyon skorları ve yan etkiler açısından belirgin farklılık saptanmadı (p> 0,05).

• **Sonuç:** Akut postoperatif ağrı tedavisinde dexketoprofen trometamolun etkinliği bu çalışmada kullanılan diğer nonopioid analjeziklerden daha üstün bulunmuştur.

• **Anahtar Kelimeler:** Deksketoprofen trometamol, parasetamol, metamizol, postoperatif analjezi, KBB cerrahisi. **Nobel Med 2010; 6(2): 47-52**

INTRODUCTION

Adequate postoperative pain management is challenging for practitioners despite recent advances in pain control techniques and analgesic agents. Effective postoperative pain management can reduce postoperative pain-related complications and decrease the cost and duration of hospitalization by enabling early mobilization.1-3 Opioid and non-opioid analgesics are commonly used for postoperative pain relief. An increase in the incidence and severity of adverse effects associated with effective opioid dosages may limit their administration resulting in inadequate pain management. In addition, use of non-opioid analgesics for postoperative pain management has become widespread, especially considering the availability of injectable formulations. The high tolerability of non-opioid agents and their relatively rare and less severe adverse effects are the major advantages when compared with opioids.[1,2]

Dexketoprofen trometamol is a newly developed NSAID belonging to the aryl-propionic acid group. It is a water-soluble salt of the S (+)-enantiomer of the racemic compound ketoprofen.[4,5] It has been widely demonstrated in preclinical studies that the anti-inflamatory and analgesic effect of ketoprofen is due entirely to the S (+)-enantiomer (dexketoprofen), while the R (-)-enantiomer is devoid of such activity.[5] Animal models of inflammation and analgesia have shown that dexketoprofen trometamol is at least twice as potent as the parent compound ketopropen.[6] In humans, the analgesic efficacy of dexketopropen trometamol using an oral formulation has been demonstrated in pain full conditions such as dental pain.[7] Currently, there are few available dexketopropen trometamol that can be used parenterally, which is the preferable rotue of administration in the immidiate postoperative period. Paracetamol is a non-opioid agent, and it is believed that it primarily acts upon the central nervous system by way of central cyclooxygenase inhibition, and probably has an indirect influence on the serotoninergic system. Paracetamol has a good safety profile and easily passes through the brain barrier, which assures it as an effective analgesic.[8] Metamizol, another non-opioid analgesic, has plasma elemination half-life of 3-4 h.[9] It has minor adverse effects and powerful pain-relieving antipyretic and spasmolytic properties.

Ear, nose and throat (ENT) surgery usually pose much postoperative discomfort due involvement of the airways or hearing system. Studies have demonstrated that postoperative paracetamol and metamizol can significantly reduce postoperative pain and improve the quality of recovery after ENT surgery.[9-11]

However, there are no direct comparisons of the efficacy of dexketoprofen trometamol with paracetamol and metamizol. We therefore designed the present study to assess the analgesic effects of dexketoprofen trometamol and two other injectable non-opioids, paracetamol and metamizol, for postoperative pain relief in patients undergoing ENT surgery. →

MATERIAL and METHOD

After Institutional Ethics Committee approval and patients' written consent, 90 patients aged between 18-65 years, ASA I-II and undergoing elective ENT surgery were enrolled into the study protocol. Nasal/sinus surgery, otologic surgery and head/neck surgery were performed on the patients (Table 1) between February and May 2009 in Tepecik Education and Research Hospital, Izmir. Patients were excluded if they had received any analgesic medication within 12 h before surgery, were pregnant, breast-feeding, were allergic to any of the medications used in the study, had a history of drug abuse, or clinically significant cardiovascular, renal, hepatic, or gastrointestinal disease.

One day before the operation, patients received instructions about the visual analog scale (VAS; 0= no pain and 100= worst pain imaginable) and verbal rating scales (VRS; 0=no pain, 1=slight pain, 2= moderate pain, and 3=severe pain) for pain. Patients were randomly assigned to 1 of 3 treatment groups; Group D (n=30), dexketoprofen trometamol; Group P (n=30), paracetamol and Group M (n=30) metamizol. All medicines were prepared by a nurse who had no other involvement in the study. None of the patients and managing anaesthetists were aware of the randomization code. The first dose of all drugs listed below was given after skin closure:

Dexketoprofen trometamol: an initial intravenous (i.v.) dose of 50 mg was given at the end of surgery; that dose was repeated twice with an 8-hour interval.

Paracetamol: an initial i.v. dose of 1 gr was given at the end of surgery; that dose was repeated 6 h,12 h and 18 hours later.

Metamizol: an initial i.v. dose of 1 gr was given at the end of surgery; that dose was repeated twice with an 8-hour interval.

On arrival at the preanesthetic room, standart monitoring equipment consisting of electrocardiography, noninvasive blood pressure monitoring, finger pulse oximetry was installed. A standardized general anesthetic was used. Induction was achived with 10°g/kg atropine, 1 °g/kg fentanil, 5 mg/kg thiopental. Rocuronium (0.6 mg/kg) was given to facilitate orotracheal intubation. Maintenance of anesthesia consisted of sevofurane 1.5-2% (end-tidal) and 60% nitrous oxide in oxygen. At the completion of skin closure, muscle relaxation was reversed and patients extubated. The ENT surgeons and residents used the standard surgical techniques to perform the surgery. After tracheal extubation, patients were transferred to the PACU. Pain was assessed using VAS and VRS at 1 h, 2 h, 3 h, 4 h, 6 h, 12 h, and 24 h after surgery. Pethidine (1 mg/kg) was given intramuscularly to patients whose pain score (VAS) was ≥ 30 mm and then recorded. Patients were evaluated for the presence of adverse events such as nausea, vomiting, dyspepsia, skin rash, headache. Nausea was evaluated using a two point scale; 0= absent, 1= positive. Metoclopramide was given in case of vomiting or after two successive episodes of nausea. The degreee of sedation was rated on a four-point scale; 0= awake, 1= drowsy, 2= asleep but rousable, 3= unrousable. All measurements were recorded by the same anesthesia resident who was blinded to the study drugs administered.

Table 1: Demographic and surgical characteristics of the treatment groups

	Group D (n=30)	Group P (n=30)	Group M (n=30)
Age (yr)	54.8±8.6	48.5±12.1	50.4±11.3
Weight (kg)	67.6±14.8	61.9±12.3	70±18.2
Duration of Surgery (min)	74.6±29.3	76.8±27.9	73.9±28.0
Gender (F/M) (n)	15/16	14/16	15/15
Surgical procedures (n)			
Nasal/sinus surgery	8	9	9
Otologic surgery	11	10	10
Head/neck surgery	1	1	1

Data are presented as means±SD. There were no significant differences among the three groups.

A power analysis was performed on the basis of difference in subjects' postoperative pain scores, as indicated by VAS. The sample size was calculated acording to previous study of postoperative pain management.[1] After having reviewed the results of previous study, we assumed in this investigation that the VAS scores of the patients decreased 30% afer administration of analgesic drugs during the postoperive period (mean VAS scores of around 23.1±4.7 in the NSAI groups, 34.1±4.3 in the paracetamol and 37.7±3.8 in the metamizol groups). A simple size of 30 patients per group was required to detect a clinically relevant 25% difference in VAS scores between dexketoprofen trometamol and other groups with a significance level of 5% and power of 90%. Statistically testing was performed using SPSS 10.0 program for Windows (SPSS Inc., Chigago, IL). Differences among the 3 groups were analyzed by an analysis of variance test or its nonparametric counterpart, the Kruskal-Wallis test. Homogeneity of variances was calculated with the Levene test Post hoc analysis was performed with the Bonferroni test. Either the X^2 or Fisher's exact test was used to analyze categorical→

Table 2: Postoperative VAS scores

h	Group D (n=30)	Group P (n=30)	Group M (n=30)	p value
1	20.3±9.6*(16.7-23.9)	44.7±11.3 (40.4-48.9)	44.3±12.2 (39.8-48.9)	0.000
2	19.3±7.8*(16.4-22.3)	35.0±11.6 (30.6-39.4)	34.3±11.6 (26.9-32.2)	0.000
3	16.3±6.1*(14.0-18.6)	27.3±10.1 (23.5-31.1)	27.3±9.8 (23.7-31.0)	0.000
4	15.3±5.0*(13.4-17.2)	23.7±8.0 (20.6-26.7)	24.0±7.7.(21.1-26.9)	0.000
5	14.3±5.6*(12.2-16.5)	20±6.4 (17.6-22.4)	20.3±7.6 (17.5-23.2)	0.001
6	12.3±5.6*(10.2-14.5)	16.3±6.1(14.0-18.6)	16.3±7.1 (13.7-19.0)	0.023
12	9.3±7.8 (6.4-12.3)	12.7±5.8 (10.5-14.8)	13.0±5.3 (11.0-15.0)	0.056
24	7.0±7.2 (4.4-9.6)	8.0±6.1 (5.7-10.3)	8.2±6.2 (7.6-11.7)	0.254

Data are presented as means±SD (95% CI) * p<0.01, versus Group P and M

Table 3: Postoperative VRS scores

h	Group D (n=30)	Group P (n=30)	Group M (n=30)	p value
1	1.07±0.36*(0.93-12.0)	2.33±0.60 (2.11-2.56)	2.03±0.76(1.75-2.32)	0.000
2	0.9±0.40* (0.75-1.05)	1.60±0.49 (1.41-1.79)	1.33±1.06 (0.94-1.73)	0.001
3	0.60±0.49* (0.41-0.79)	1.07±0.64 (0.83-1.31)	0.83±0.74 (0.55-1.11)	0.021
4	0.33±0.47* (0.15-0.51)	0.70±0.46 (0.53-0.87)	0.57±0.50 (0.38-0.75)	0.015
5	0.23±0.43* (0.07-0.39)	0.57±0.50 (0.38-0.75)	0.50±0.50 (0.31-0.69)	0.022
6	0.17±0.37* (0.03-0.31)	0.33±0.47 (0.15-0.51)	0.47±0.50 (0.28-0.66)	0.045
12	0.17±0.37 (0.03-0.31)	0.17±0.37 (0.07-0.39)	0.43±0.50 (0.25-0.62)	0.056
24	0.07±0.25 (0.03-0.16)	0.13±0.34 (0.00-0.26)	0.27±0.45 (0.10-0.43)	0.095

Data are presented as mean±SD (95% CI) * p<0.05, versus Group P and M

variables, where appropriate. Data are expressed as means ± SD. Differences were considered statistically significant at $p<0.05$.

RESULTS

There were no significant differences between the groups regarding age, body weight, gender and duration of surgery ($p>0.05$) (Table 1).

There were significant differences in VAS and VRS scores at postoperative 1., 2., 3., 4., 5.,.and 6. h in Group D with Groups P and M ($p<0.05$). VAS and VRS scores at 1., 2., 3., 4., 5., and 6. h in Group D was lower than Groups P and M, while there was no significant difference in VAS scores at 12. h and 24. h between groups (Table 2, 3). During the 24 postoperative hours, no additional opioid analgesic was required in 27 (90%) patients in Group D, 18 (60%) in Group P and 20 (66.6%) in Group M. When the sedation scores of the groups were compared, there was no statistical difference between groups.

Adverse events observed during the study and patient satisfaction are summarized in Table 4. In total, 66 adverse events were reported by 35 (53%) patients. The most commonly reported adverse events in all three groups were vomiting and nausea. All adverse events were mild to moderate in intensity and most were transient. No severe or serious adverse events were reported. There were no significant differences in the incidence of adverse events between the three treatment groups ($p>0.05$).

DISCUSSION

Postoperatif pain continues to have a major impact on the recovery process and patient satisfaction with their care after surgery. NSAIDs, paracetamol and metamizol are frequently being used for the treatment of pain after ENT surgery.[1,9-11] The results of this study revealed that administration of intravenous dexketoprofen trometamol for acute postoperative pain management resulted in a significant decrease in VAS scores 6 h after surgery and the requirement for rescue analgesia during the first 24 h after surgery when compared with paracetamol and metamizol.

This is the first study that compares dexketoprofen trometamol with the well established paracetamol and metamizol for pain relief after ENT surgery. Although all the drugs studied belong to the group of non-opioid analgesics, they act by different mechanisms. The analgesic action of parecoxib results from the inhibition of the COX-2 isoenzyme that plays an important role in the synthesis of prostaglandin E_2 in the traumatized area by increasing the threshold of activation of the nociceptors. In contrast, despite the long use of metamizol and paracetamol their mode of action is still not fully understood. Generally considered as belonging to the NSAIDs there is only a weak inhibition of prostaglandin synthesis and a lack of other typical actions of NSAIDs, such as antiplatelet activity and gastrotoxicity, suggesting a distinct mode of action.[12]

Dexketoprofen trometamol has been demonstrated to be effective in the treatment of acute pain.[13] Hanna et al[4] reported that intramuscular administered dexketoprofen trometamol 50 mg threee times daily per 24 hours is effective in the management of postoperative pain after major orthopaedic surgery and provides satisfactory pain control with relatively fewer advers effect. In this study, the mean cumulative amount of morphine used was of 39 mg in the dexketoprofen trometamol grup vs 64 mg in the placebo group. Jackson et al[7] showed that a single dose of dexketoprofen trometamol provided sufficient analgesia for the complete 24-h study period in 40% of patients in surgical dendistry. In our study, dexketoprofen trometamol provided→

sufficient analgesia for the complete 24-h study period in 90% of patients vs 60% paracetamol group and 66.6% metamizol group.

There have been conflicting reports regarding the efficacy of NSAIDs compared with acetaminophen in the management of postoperative pain. Although some investigators have reported a similar efficacy of paracetamol and the nonselective NSAIDs [14] other studies suggest [11,15] that the NSAIDs may be more effective than paracetamol in preventing pain after ENT surgery.

Metamizol has been found to be more effective than either parenteral parecoxib or paracetamol in postoperative pain management.[12] Also, Saray et al [16] reported that i.m. metamizol 1 gr three times daily was more effective than diclofenac 75 mg twice daily in providing postoperative analgesia. In contrast, Sener et al9 showed that intravenously administered metamizol 5 gr/d was not as effective as lornoxicam 24 mg/d in the management postoperative analgesia in otolaryngologic surgery. Torres et al [17] reported a comparable efficacy of metamizol compared with tramadol. Our data suggest that administration of dexketoprofen trometamol more effective than metamizol in managing acute postoperative pain treatment.

There are possible concerns regarding the side effects of the analgesics used in this study. Both metamizol and paracetamol are reported to cause hypotension that may be poorly tolerated by critically ill patients.[18] In contrast, based on the results obtained in the present study, the three study drugs were well tolerated in this relatively healty population. The most common adverse effects reported by patients during the first postoperative 24 hours in this study were nausea (26.6-33.3%) and vomiting (13.3%-20%) side effect. Postoperative nausea and vomiting (PONV) are common postoperative problems following general anesthesia. Use of opioid analgesics is an important factor in increasing risk of PONV.[19] In our study, use of opioids as rescue analgesics occurred more frequently in the paracetamol and metimazol groups when compared with the dexketoprofen trometamol group. However, there were no significantly differences between the groups for PONV. Metimazol can cause agranolocytosis. Nevertheless, other nonopid analgesics might also have caused agranulocytosis. Metimazol has been withdrawn in Sweden and some other countries because of this adverse effect. We did not encounter any complication related to metamizol.

Table 4: Adverse events

	Group D (n=30)	Group P (n=30)	Group M (n=30)
Nausea	8 (26.6%)	10 (33.3%)	9 (30%)
Vomiting	4 (13.3%)	6 (20%)	5 (16.6%)
Dyspepsia	1 (3.3%)	1 (3.3%)	0
Skin rash	1 (3.3%)	0	0
Headache	6 (20%)	8 (26.6%)	7 (23.35%)

Values are number (n) and percentages (%). No significant differences were found between the groups.

This study can be critized for the type of surgical procedures chosen for this analgesic study. Although ENT surgery might not be considered an operation that is associated with a frequent incidence of severe postoperative pain. Also, in our study, the lack of a placebo group may of course be questioned; however, Issioui et al [20] reported that 50% of the patients in the placebo group experienced moderate-to-severe pain in the early postoperative period in patients undergoing ENT surgery. Furthermore, previous studies have demonstrated that pain after ENT surgery is an acceptable model for studying non-opioid analgesics.

In conclusion, in patients undergoing ENT surgery, the intravenous administration of dexketoprofen trometamol 150 mg/d provides significantly better pain control in the early postoperative period compared with paracetamol 4 gr/d or metamizol 3 gr/d without increasing adverse side effect.

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