The Evaluation of Safety and Analgesic Efficacy of Paracetamol and Ibuprofen Followed by Impacted Third Molar Surgery

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ABSTRACT

***Aim**: The aim of this prospective, randomised, single-blind, single center, parallel group study was to compare the analgesic effects and safety of a single starting dose of soluble ibuprofen and 2 g of intravenous paracetamol for postoperative pain management in patients undergoing surgical removal of lower impacted third molar.*

***Method**: 30 patients who referred for surgical removal of bilateral impacted lower third molar teeth were included in the study. The patients were divided in to two groups. In the early preoperative period, the patients received a single starting dose of either soluble ibuprofen 400 mg dissolved in 100 ml of water or 15-min intravenous infusion of paracetamol 2 gram. Surgery in each patient was performed twice, 1 impacted tooth was being removed at a time and another one was being removed 2 weeks later. Trismus, safety variables and hepatotoxicity and analgesic efficacy were evaluated.*

***Result**: The analgesic efficacy over a 24-hour period was of statistically no significant difference between 2 groups but clinical data shows that the analgesic efficacy of paracetamol group was greater than ibuprofen group. As for the mean trismus values, there was no statistically significant difference between groups. The administered dosages of the analgesics did not lead to hepatocellular injury and biochemical abnormality.*

***Conclusion**: Consequently, both administered dosages of drugs can safely be used as a single starting doses. In order to obtain more better results with analgesic efficacy and safety in use, more trials are needed for administering higher doses of paracetamol and ibuprofen.*

***Key words:** Preemptive analgesia, impacted third molar surgery, hepatotoxicity, analgesic efficacy*

Gömülü Üçüncü Molar Diş Ameliyatı Öncesinde Uygulanan Parasetamol ve İbuprofenin Ağrı Kesici Etkinliği ve Güvenliği Açısından Değerlendirilmesi

Amaç: *Bu prospeftif, rastgele, tek-kör, tek merkezli, paralel grup çalışmasının amacı üçüncü molar diş ameliyatları geçiren hastaların ameliyat sonrası ağrı kontrolünde ameliyat öncesinde tek doz çözülebilir ibuprofen veya 2 gram damariçi parasetamol uygulanmasının güvenlik ve ağrı kesici etkinliği açısından kıyaslanmasıdır.*
Metod: *Çalışmamıza, çift taraflı gömülü 20 yaş dişlerinin ameliyatla çıkarılması gereken 30 hasta dahil edilmiştir. Hastalar 2 eşit gruba ayrılmıştır. Erken ameliyat öncesi dönemde, hastalar tek başlangıç doz olarak ya 100ml içinde çözünmüş 400mg ibuprofen ya da 15 dakikada damariçi infüzyon yoluyla 2gr paracetamol aldılar. Her hastada cerrahi 2 kez uygulandı, ilk cerrahide uygulanan bir taraftan 2 hafta sonrasında diğer tarafın ameliyatı uygulandı. Güvenlik değişkenleri, ağız açıklığındaki kısıtlılık, karaciğer zehirlenmesi ve ağrı kesici etkinliği değerlendirildi.*
Bulgular: *Ameliyat sonrasındaki ilk 24 saatlik süre içerisinde ağrı kesici etkinlik açısından her iki grup arasında istatistiksel anlamda bir fark gözlenmemekle birlikte klinik göstergelere göre parasetamol grubu ibuprofen grubundan ağrı kesici etkinliği açısından daha etkin bulunmuştur. Ağız açıklığında kısıtlılık konusunda ise, gruplar rasında herhangi bir istatistiksel fark gözlenmemiştir. Ağrı kesicilerin uygulanan dozları karaciğer hasarı ve biyokimyasal anormalliğe yol açmamıştır.*
Sonuç: *Neticede, her iki uygulanan ilacın dozları başlangıç tek doz olarak kullanılabilir. İlaçların kullanımı açısından ağrı kesici etkinliği ve güvenlikte daha iyi sonuçlar elde etmek için, parasetamolün ve ibuprofenin daha yüksek dozlarının uygulandığı çalışmaların yapılmasına ihtiyaç vardır.*
Anahtar kelimeler: *Preop ağrı kesici etkinlik, gömülü 3. molar ameliyatı, karaciğer zehirlenmesi*

INTRODUCTION

The removal of third molar teeth in a day case setting has become popular with patients, healthcaretrusts and oral surgeons (1). An increasing number of studies have focused on the use of preemptive analgesia for postoperative pain relief. It has been found that pain scores immediately after surgery are significantly improved with the use of preemptive analgesia. NSAIDs (nonsteroid antiinflammatory drugs) and other nonopioid analgesics are commonly used for postoperative pain relief in ambulatory surgery (2).

Ibuprofen is a peripherally acting nonsteroidal anti-inflammatory agent which has been used in the treatment of classical rheumatism for over 10 years. It has also been shown to have analgesic properties in the treatment of soft tissue injuries, dysmenorrhoea and postoperative pain following oral surgery (3). Studies have found that a soluble ibuprofen preperation provided an earlier onset of analgesia than ibuprofen tablets in patients with postoperative pain after third molar surgery (4).

Ibuprofen, a commonly used over-the-counter analgesic, is as effective as rofecoxib for the relief of acute postoperative pain following third molar surgery when used preemptively (5). The use of a first higher dose of analgesics in the immediate postopertive period becomes more and more frequent in order to prevent the occurence of pain when anesthetic effect wears off (6). Zacharias et al. (7) have found that no clinical and statistically difference with comparing the efficacy and safety of single oral doses of 60mg/kg and 90mg/kg paracetamol prior to surgical removal of mandibular third molar. So far a starting dose of 2 g of IV paracetamol has not been recommended, but some findings suggest its use would be possible. In addition, the maximal concentration reached after administration of 2 g of IV paracetamol in healthy subjects (ranging from 235 and 521 mmol/L) stays far below the 1000mmol/L determined as threshold for a potential hepatotoxicity. Juhl et al. (6) also noted that with administration of 2g paracetamol lead to temporary increase in ALT and AST levels which might be the signs of hepatotoxicity. Page noticed that drug administration in similar doses may lead to increase in aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH) and bilirubin and decrease in protrombine levels (8). Primary outcome measures are analgesic efficacy, trismus and hepatotoxic effects. Secondary outcome measure are adverse effects of administered drug doses.

The aim of this prospective, randomised, single-blind, parallel group study was to compare the analgesic effects and safety of a single starting dose of soluble ibuprofen and 2 g of intravenous paracetamol for postoperative pain management in patients undergoing surgical removal of lower impacted third molar.

MATERIALS AND METHODS

The study was completed in a single center at the Faculty of Dentistry, University of Selcuk, Konya, Türkiye between December 2006 and April 2007 after approval by the Ethical Committee at the University Hospital, Konya, and written informed consent was obtained from all patients.

30 patients (15 women, 15 men) who referred for surgical removal of bilateral impacted lower third molar teeth were included in the study. The patients were classified as American Society of Anesthesiologists (ASA) risk class I, II, or III and who were suffering from moderate to severe pain (assesed on a Visual Analog Scale) within 24 hours after surgery were randomised into the study. Patients were excluded from the study for the following reasons: other painful physical conditions which might confound pain assesment, liver or advanced renal dysfunction, psychiatric or medical conditions that might impair communication or compliance with the study procedures, known drug abuse, contra-indications to the study drugs, had taken any NSAID (other than aspirin in a dose of 150 mg daily or less) within 24 h of the operation, concomitant use of sedatives or microsomal enzyme inducers, pregnant women or women of childbearing potential not using adequate contraception, under 16 yr old, weighed 50 kg, had taken acetaminophen or acetaminophen containing medicines within 12 h of the operation, taking an angiotensin-converting enzyme inhibitor, warfarin, steroid (other than interoperative dexamethasone), or any immunosuppressive drug, were intolerant to any NSAID or acetaminophen, suffering from a severe local infection, had a history of peptic ulceration, asthma, or severe haemopoetic, renal or hepatic disease, were participating in the investigation of another experimental agent, or if the clinician believed for any other reason that participation in the study might not be in their best interests.

The study was conducted as a prospective, single-centre, parallel group, single-blind and randomised. In the early preoperative period, the patients received a single starting dose of either soluble ibuprofen 400 mg dissolved in 100 ml of water or 15-min intravenous infusion of paracetamol 2 gram. Each patient received both treatments in random and the patients were randomly allocated to one of two groups according to sealed enveleopes. The surgeon was unaware of which drug had been given preoperatively. An experienced surgeon did the operations under local anesthesia. Surgery in each patient was performed twice, 1 impacted tooth was being removed at a time and another one was being removed 2 weeks later. The patients were operated using a standard technique, which included a horizontal incision at the midline of the mandibular ramus was made and extended anteriorly to include the gingival crevice of the mandibular second molar tooth without vertical incision following raising a mucogingival flap and removal of bone with a saline-cooled bur in a surgical drill. During the trial period, the patients abstained from the coffee, tea, or caffeine-containing beverages. Alcohol was not allowed from 12 hour before drug administration and until 48 h after medication. Local anestehesia only (inferior alveolar, lingual, and buccal nevre blocks maintained using 2 ml of articaine hydrochloride 40mg/ml with epinephrine hydrochloride 0.006 mg/ml) was used during standardized surgery procedures.

Patients were enrolled if their postoperative pain intensity reached at least 40 mm on a 100-mm Visual Analog Scale (VAS) where 0=no pain and 100= worst possible pain, within 6 hour after surgery. Baseline assessments of pain intensity were made just before administration of trial medication. Postreatment observations began simultaneously with drug administration (To). Pain intensity (PI) were assessed at baseline (To, start of infusion) and at 15 min, 30 min, 45 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 16 h and 24 h postmedication. Participants were asked to rate their pain on 100 mm VAS, printed one per double page in a booklet they took home. Ratings were requested at baseline defined points. In case of interrupted infusion, the reason, time of interruption and time of restarting were recorded. All patients were prescribed with 400mg ibuprofen tablet form with 12 hour intervals for 5 days postoperatively with starting to intake first analgesic when the patient have moderate to severe pain. Safety variables comprised general and local adverse events (AEs), vital signs (arterial blood pressure and heart rate) and laboratory variables (hematology and plasma biochemistry.

Adverse effects including nausea, vomiting, allergy, and bleeding from the surgical site were assessed before surgery on day 0 up to day 7. Vital signs were measured at just prior to ratings and medication and at 1 hour medication. Blood samples for laboratory variables were drawn within 6 days before surgery and 48 h postmedication.

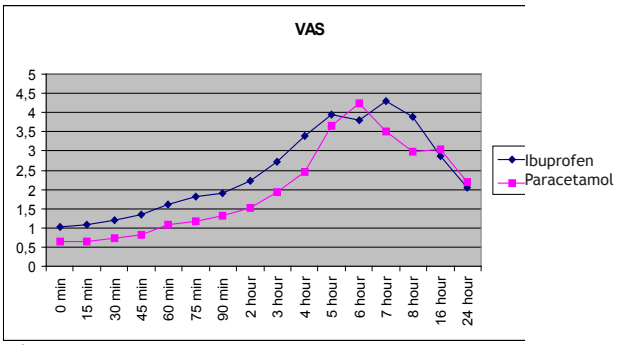

Figure 1. *The comparison of pain intensity levels in both groups*

Trismus values were measured at just before the drug administration, 2nd day and 7th day after the operation. Aspartate transaminase (AST; EC 2.6.1.1), alanine transaminase (ALT; EC 2.6.1.2) and lactate dehydrogenase (LDH; EC 1.1.1.27) levels were measured by enzymatic kinetic method on LX20 Beckman Coulter autoanalyzer.

Statistical Analysis

SPSS 11.0 for Windows was used. Student T-test was used to compare the groups and also the comparison of pain intensity levels, trismus values and biochemical variables of 2 groups were analysed by independent Student t-test. Significant difference was pointed at 0.05.

Table1. *The mean VAS values for each group*

	Ibuprofen	*Paracetamol*	*p value*
V0min	*1.0227±1.4558*	*0.6387±0.6302*	*0.192*
V15min	*1.0843±1.5564*	*0.6463±0.6004*	*0.159*
V30min	*1.1940±1.3707*	*0.7313±0.6035*	*0.098*
V45min	*1.3537±1.3176*	*0.8303±0.6558*	*0.058*
V60min	*1.6203±1.2945*	*1.0690±0.7615*	*0.050**
V75min	*1.8273±1.2959*	*1.1553±0.9773*	*0.027**
V90min	*1.8893±1.2129*	*1.3077±1.0880*	*0.055*
V2hour	*2.2333±1.1547*	*1.5263±1.2311*	*0.025**
V3hour	*2.7273±1.2698*	*1.9343±1.2638*	*0.018**
V4hour	*3.4063±1.4035*	*2.4667±1.3958*	*0.012**
V5hour	*3.9410±1.8986*	*3.6413±1.2742*	*0.476*
V6hour	*3.7950±1.4635*	*4.2297±1.7143*	*0.295*
V7hour	*4.2983±1.8665*	*3.5150±1.7180*	*0.096*
V8hour	*3.8913±2.2409*	*2.9693±1.7073*	*0.079*
V16hour	*2.8527±1.7229*	*3.0320±1.7890*	*0.694*
V24hour	*2.0453±1.6237*	*2.1813±1.9130*	*0.768*

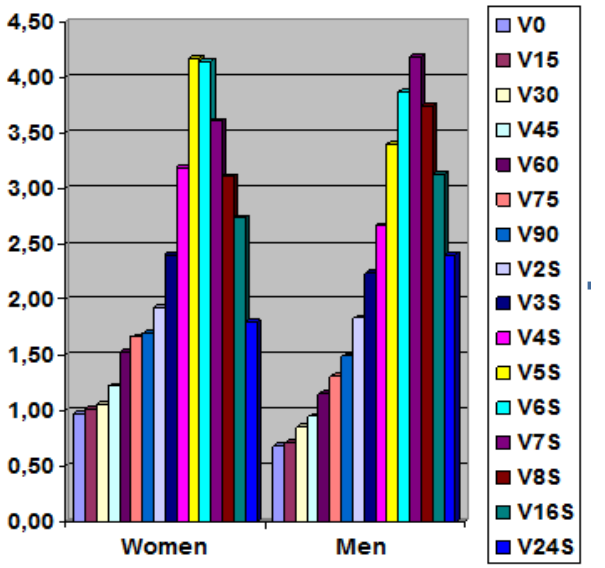

Figure 2. *The mean VAS scores according to the gender*

RESULTS

In the duration of 4 months of this study (half of December 2006 to the half of March 2007). All 30 patients (mean age 21.1 years, range 18-25) were evaluated for analgesic efficacy, trismus and for safety. The operation times and baseline pain scores were similar for each treatment. The mean operation time of the ibuprofen group and paracetamol group is 15.6 minutes and 15.2 minutes, respectively.

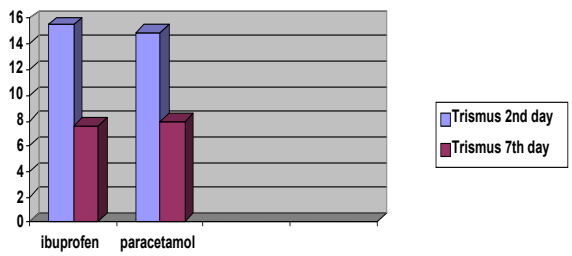

Figure 3. *The comparison of mean trismus values*

Table 2. *The group mean trismus values in 2nd and 7th days*

	Ibuprofen	*Paracetamol*	*p value*
Trismus 2nd day	*15.43±9.12*	*14.83±9.03*	*0.799*
Trismus 7th day	*7.53±1.54*	*7.93±1.39*	*0.848*

Pain scores after the treatment with soluble ibuprofen and intravenous paracetamol are shown in Table 1. The analgesic efficacy over a 24-hour period was of statistically no significant difference between IV paraceamol 2 gr group and the soluble ibuprofen group. Statistically no significant difference was found in mean VAS scores after operation (Table 3). But clinical data which were obtained with questionairres did not support the statistical data. Clinical data shows that the analgesic efficacy of paracetamol group was greater than ibuprofen group. The pain intensity levels in paracetamol group was higher than in ibuprofen group. The mean time for requirement of rescue analgesic in paracetamol group is 6 h 20 minutes, in ibuprofen group is 5 h 41 minutes after the initial drug intake (Figure 1). There was no statistically significant difference in gender between 2 groups ($p>0.05$) The mean VAS scores of each gender was shown in Figure 2. As for the mean trismus values, there was no statistically significant difference between groups ($p>0.05$). The mean trismus values in the 2nd and 7th day were shown in Table 2. The comparison of mean trismus values for both groups were shown in Figure 3.

General and local adverse events, vital signs, and laboratory analysis were included for the evaluation of the safety of analgesic drugs. Vital signs were measured at 3 time points such as at just before the analgesic intake, before the operation and at 1 hour after the operation. Vital signs were observed in normal limits. The most frequent adverse events were associated with the surgery (surgical site recation, hemorrhage, operation site inflammation). Of the 30 patients, as for the evaluation of adverse events within 2 days subsequent to the operation, no adverse events were observed in 26 patients. There was no local pain at the infusion site, surgical site reaction, hemorrhage in patients with paracetamol group. 1 patient with headache, fever and tachycardia were observed in paracetamol group. 1 patient with nausea in the first day, 1 patient nausea in the second day and 1 patient with diarrhea were clinically observed. There was no serious adverse events and no patient was withdrawn because of an AE.

As for the evaluation of hepatocellular injury and biochemical abnormality AST, ALT and LDH values were analysed, consequently the administered dosages of the analgesics did not lead to hepatocellular injury and biochemical abnormality and no increase in AST, ALT and LDH values were reported in both groups.

DISCUSSION

The quality of life following impacted third molar surgery is well in younger patients and Gunbay and Gomel (9) suggested the removal of impacted third molars must be performed in younger ages because of the increased incidence of complications in the older ages (10). Therefore in this study, the young patients (18-25) were included. For this reason, we considered that there were no serious complications observed after impacted third molar surgery.

Preemptive analgesia prevents establishement of central sensistisation caused by incisional and inflammatory injuries (11). In the oral surgery literature, Dionne and Cooper (12) stated that administration of preemptive analgesic drugs provide a delay for onset of pain or decrease the level of pain intensity after surgical removal of third molars. Prodrug of paracetamol that can be administered parenterally when greater efficacy or a fast onset of analgesia is desirable. IV infusion of propacetamol 2 g was significantly more effective than paracetamol 1 g taken orally in patients with moderate to severe postoperative pain after hallux valgus surgery (13,14). There are conflicting results concerning preemptive and preventive administration of different groups of analgesics. Preventive analgesia was considered to be a suitable definition of both the preoperative and intraoperative administration of drugs for preventing the pain before its onset after surgical procedures (15-17). Based on this knowledges, the analgesic drugs were administered 30 minutes before the surgery. In this way, it was estimated that the time for requirement of rescue analgesic will be longer and the need for total amount of additive analgesic drugs will be decreased postoperatively. As a result, the patients stated that the need for first rescue analgesic was a long period later subsequent to the operation. And also, beside analgesic efficacy, the preemptive analgesic use may subside the patient physcologically and thus the patients may partially get rid of serious concern about to have experience of pain.

In order to determine and evaluate the efficacy and pain intensity levels of analgesic drugs after the impacted third molar surgery, mostly VAS has been used (18). The time points for measuring VAS may change. Increased time points for measuring with VAS determine detailed information. McGurk et al. (19) determined the time points at 10, 20, 30 ve 40. minutes and 1, 1.5, 2, 3,

4, 5 ve 6. hours. Joshi et al. (1) determined the time points at 15. ve 30. minutes, 1. and 3. hours. Jackson et al. (20) determined at 8. and 24. hours. Juhl et al. (6) 0., 15., 30., 45.minutes, 1, 2,3,4,5,6,7 and 8.hours. For this reason, in this study, the patients were informed to fill up the VAS at 0., 15., 30., 45., 60., 75., 90. minutes and 2., 3., 4., 5., 6., 7., 8., 16., 24. hours.

Seymour et al. (21) reported that sensitivity and tolerance of pain intensity varies in gender, thus women perception of pain sense is more intense than in men, the reason why the behaviours of the women are more sensitive for evaluation of pain severity than in men. In our study, there was no difference between each gender. Drug instructions stated that the need for rescue analgesic is in ibuprofen group and paracetamol group, 4 hours and 4-6 hours, respectively. In our trial groups, while the patients need the rescue analgesic with an average of 6.2h postoperatively in the paracetamol group, the patients need the rescue analgesic with an average of 5.41h postoperatively in the ibuprofen group. Eventhough analgesic efficacy of both groups statistically no differ from each other, on the other hand, clinically postoperative analgesic efficacy of preoperatively used paracetamol was higher than ibuprofen.

As for the evaluation of trismus, Waseem et al. (22) reported that the amount of mouth opening following impacted third molar surgery with less than 25mm shows trismus criteria. Bamgbose et al. (23) measured the trismus values at 1st, 2nd and 7th days after surgery. Pederson (24) measured at 2nd and 7th days postoperatively. In our study, the degree of trismus was evaluated with measuring the maximal mouth opening at 2nd and 7th days postoperatively. No significant difference was found between paracetamol and ibuprofen groups for the evaluation of trismus. The amount of maximal mouth opening at 7th day increased in comparison with the 2nd days measurements in each group and it was statistically significant

Drug adverse events were observed clinically for the first 48 hours. 1 patient with adverse effect in paracetamol group. 3 patients with the adverse effects in ibuprofen group. The adverse effects of the 3 patients were considered to be associated with the additive doses of ibuprofen rather than single dose of ibuprofen which administered preoperatively. There was no significant difference between groups regarding safety. Drugs that damage the liver account for 9.5% of all suspected adverse drug reactions (25). Because of its frequency and severity, drug-induced liver disease is an important aspect of clinical practice. More than 600 medications have been associated with liver injury (26). Despite this common usage of these drugs, our knowledge of analgesic pharmacodynamics remains limited (27).

As for the hepatotoxicity, blood samples were drawn at different time points. Schoonen et al. (28) drawn at before drug administration and at 24th hour postmedication in an animal study. Juhl et al. (6) measured within 6 days before surgery and 48 h postmedication. In this invivo study, in compatible with the literature review, blood samples for laboratory variables were drawn at premedication and 48h postmedication.

Waters and Riely (26) reported that elevation mildly of AST and ALT activity may lead to hepatocellulary injury. Goldkind and Laine (29) suggested that ALT elevations alone do not reliably signal serious hepatotoxicity, elevated ALT and AST may be predictors of an increased risk of acute liver failure. Page (8) reported the simultaneously decreasing of protrombin time with increasing hepatic transaminase (AST, ALT), LDH and bilirubin levels. In this trial groups, pre- and postmedication ALT, AST and LDH values which are the predictors of diagnosis of liver injury were analysed. In this study, both drugs did not lead to biochemical abnormality and hepatocellular injury.

In conclusion, despite there was no statistically different between paracetamol and ibuprofen, clinically paracetamol has better analgesic efficacy. There was no statistically difference in gender with trismus in both groups. The administered dosages of analgesic drugs have no adverse effects such as biochemical abnormality and hepatocellular injury.

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