Original Article

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Efficacy Comparison of Ibuprofen 400 Mg and 800 mg in the Treatment of Renal Colic: Prospective Randomized Double-blind Clinical Study

Renal Kolik Tedavisinde İbuprofen 400 Mg ve 800 Mg'nin Etkinlik Karşılaştırması: Prospektif Randomize Çift-kör Klinik Çalışma

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ABSTRACT

Objective: Renal colic, predominantly due to ureteral stones, constitutes a significant portion of urinary system-related hospital admissions. Non-steroidal anti-inflammatory drugs, notably ibuprofen, are favored over opioids for pain management. However, the optimal intravenous (IV) ibuprofen dosage for renal colic remains unclear. This study aimed to compare the analgesic efficacy of IV ibuprofen at doses of 400 mg and 800 mg in moderate to severe renal colic patients.

Methods: A multicenter, prospective, randomized, double-blind controlled clinical trial was conducted on patients with moderate to severe renal colic. Patients meeting inclusion criteria were randomly assigned to receive either 400 mg or 800 mg IV ibuprofen. Pain scores were assessed using numeric rating scale at baseline, 15, 30, 60, and 120 minutes. The need for rescue analgesics and occurrence of side effects were recorded.

Results: Out of 150 initially enrolled patients, 126 completed the study. Pain reduction was more significant in the 800 mg group compared to the 400 mg group, especially at the 120-minute mark ($p<0.05$). The need for rescue analgesics and occurrence of side effects did not significantly differ between the two groups.

ÖZ

Amaç: Üreter taşlarına bağlı olarak ortaya çıkan renal kolik, üriner sistemine ilişkin acil servis başvurularının önemli bir kısmını oluşturur. Bu durumda ağrı yönetimi, non-steroidal anti-enflamatuvar ilaçlar arasında yer alan ibuprofen gibi ilaçların opioidlere tercih edilmesiyle gerçekleştirilir. Ancak, renal kolik için en etkili intravenöz (IV) ibuprofen dozu hala netlik kazanmamıştır. Bu çalışmanın amacı, orta ila şiddetli renal koliği olan hastalarda IV ibuprofenin 400 mg ve 800 mg dozlarının analjezik etkinliğini karşılaştırmaktır.

Yöntemler: Orta ila şiddetli renal koliği olan hastalarda çok merkezli, prospektif, randomize, çift-kör kontrollü klinik bir çalışma gerçekleştirilmiştir. Dahil edilme kriterlerini karşılayan hastalar, rastgele olarak ya 400 mg ya da 800 mg IV ibuprofen almışlardır. Ağrı skorları, başlangıçta ve 15, 30, 60 ve 120 dakika sonra sayısal değerlendirme skalası kullanılarak değerlendirilmiştir. Kurtarıcı analjezik kullanımı ve yan etki görülme durumları kaydedilmiştir.

Sonuç: Başlangıçta 150 hasta dahil edilmiş olup, çalışmayı 126 hasta tamamlamıştır. Ağrı azalması, özellikle 120. dakikada, 800 mg grubunda 400 mg grubuna göre daha belirgin olmuştur ($p<0,05$). Kurtarıcı analjezik kullanımı ve yan etki görülme durumları ise iki grup arasında anlamlı bir fark göstermemiştir.

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ABSTRACT

Conclusion: This study suggests that IV ibuprofen at a dosage of 800 mg provides more effective analgesia for renal colic compared to 400 mg. Therefore, the higher dosage may be preferred in clinical practice due to its superior efficacy and safety profile. Further research could explore the long-term effects and optimal dosing regimens of IV ibuprofen in renal colic management.

Keywords: Renal colic, ibuprofen, pain management

ÖZ

Sonuç: Bu çalışma, orta ila şiddetli renal koliği olan hastalarda IV ibuprofenin 400 mg ve 800 mg dozlarının karşılaştırılmasını içermekte olup, 800 mg dozunun daha etkili bir analjezi sağladığını göstermektedir. Bu nedenle, klinik uygulamada daha yüksek dozun tercih edilmesi, üstün etkinlik ve güvenlik profili nedeniyle düşünülebilir. Gelecekteki çalışmalar IV ibuprofenin uzun vadeli etkilerini ve optimal dozaj rejimlerini daha ayrıntılı olarak araştırmalıdır.

Anahtar Kelimeler: Renal kolik, ibuprofen, ağrı yönetimi

Introduction

Pain originating from the renal tract accounts for approximately 75% of hospital admissions related to the urinary system (1). Among the most commonly identifiable causes of obstruction, ureteral stones are prominent, with more than 75% of them spontaneously passing without the need for any intervention (1,2). These complaints are observed in men at a rate of approximately 12%, whereas among women, it shows an equal distribution. Additionally, the most common age range for occurrence is between the 4th and 6th decades for men, while for women, it occurs toward the end of the 2nd decade and the beginning of the 3rd decade. Presentation rates vary according to geographical regions and seasonal periods, with an increased frequency noted in hot climates and during the summer months (3). In the pathophysiology, it is believed that the increase in prostaglandin synthesis plays a role. In this case, there is an increase in arterial vasodilation, vascular permeability, and consequently, edema and spasmodic pain occur in the ureter (1). It has been noted that paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are more effective in the treatment of renal colic compared to opioids (4). The mechanisms of pain relief by NSAIDs in renal colic are thought to involve the suppression of increased prostaglandin synthesis, reducing glomerular filtration and pressure, and decreasing stimulation of stretch receptors in that region (5,6). Additionally, there is evidence of direct effects of NSAIDs on smooth muscles (5).

In renal colic patients, a commonly used stone scoring system is frequently employed to establish the diagnosis of obstructive renal stones (7). This scoring system includes 5 main factors: gender, time, race, nausea/vomiting, and the presence of red blood cells in the urine, resulting in a total of 13 possible points. Patients' likelihood of having a stone is calculated based on the total score on a 13-point scoring system, categorized as low (0-5), moderate (6-9), and high risk (10-13) (2). Although there have been pain studies related to renal colic, there are few studies in the literature conducted using ibuprofen. Specifically, due to the routine use of two doses of ibuprofen based on physician's or patient's discretion, it was planned to compare these doses and evaluate whether there were differences in terms of potential side effects, efficacy, and safety. If there was no difference in analgesic efficacy between the two doses, we hypothesized that 400 mg might be more appropriate, and we planned to compare the 400 mg and 800 mg preparations from this perspective.

Methods

Study Design and Setting

The research was designed as a multicenter, prospective, randomized, double-blind controlled clinical study. The study was conducted by including patients with moderate and severe renal colic complaints [numeric rating scale (NRS) >4] and a stone scoring of >5 points who presented to the emergency departments of two tertiary level hospitals. Approval was obtained from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (decision number: 2, date: 27.10.2022). All patients participating in the study were informed, and written informed consent was obtained in accordance with the principles of the Helsinki Declaration for Good Clinical Practice. This study adheres to the CONSORT guidelines.

Patient Selection

Patients who presented to both emergency departments with complaints of renal colic, NRS >4, and stone score >5 were included in the study. The study included patients aged 18-65 who were diagnosed as having stones on computed tomography, hemodynamically stable, without any comorbidities, without a history of adverse reactions to the drugs to be used in the study, conscious, fully oriented and cooperative, with no differential diagnoses considered, planned for discharge to home, and willing to participate in the study.

Patients who were not willing to participate in the study, patients in whom NRS-15 and subsequent pain scores could not be obtained and patients who were pregnant or breastfeeding, allergic to any of the drug groups under study, had any contraindications related to the use of these drugs, had other comorbidities, were not planned for discharge, had any additional diseases (hypertension, kidney failure, liver disease, chronic obstructive pulmonary disease, heart failure, diabetes, etc.), had used analgesic drugs within the last 6 hours, were mentally retarded and uncooperative, had hearing impairments, and had underlying organic neurological and psychiatric disorders were excluded from the study.

Sample Size

The sample size was determined using G*Power 3.1 software. According to the sample size calculation based on the study by Cenker et al. (8), with a power of 80% and a type-1 error rate of 1%, a minimum sample size of 23 patients per group was calculated. Taking into consideration potential data losses and patients who might drop out during follow-up, we planned to enroll 75 patients in each group, resulting in a total of 150 patients (n=150).

Intervention

Randomization was performed by the principal investigator. After eligible patients were included according to the criteria by the researchers, comprehensive medical histories were taken, and vital signs at the time of admission were examined and recorded. The randomization table was created using the website https://www.randomizer.org/. Patients were assigned to groups in a 1:1 ratio. Fifteen block randomizations were conducted for each medication dose group, with 10 patients in each group. Each code and the corresponding ibuprofen dose (400 mg, 800 mg) were written on paper and placed in opaque envelopes. The envelopes were sequentially numbered to indicate the order in which they should be opened. Blinded nurses prepared the ibuprofen doses by opening the envelopes. The study nurse added the ibuprofen dose from the envelope to 100 mL of saline solution and then handed the prepared treatment to the attending nurse. The treatment was administered to the patient as a rapid infusion, not exceeding 5 minutes. In this way, the patient, the physician, and the administering nurse remained unaware of the treatment dose. Case report forms and the NRS scores contained within were filled out by these blinded physicians. The remaining 120-minute study period was completed. Patients were monitored for 120 minutes, and if there was no improvement in pain score by the 30th minute or if NRS >4 was observed at the 60th minute, the rescue treatment protocol was initiated, adding 100 mg of tramadol hydrochloride to 500 mL of saline solution. Parameters such as vital signs, NRS scores, stone scores, and the occurrence of side effects were recorded at baseline (0 minutes), 15, 30, 60, and 120 minutes.

Outcomes

The primary outcomes of the study included pain scores at the following time points: baseline (0 minutes), 15 minutes, 30 minutes, 60 minutes, and 120 minutes. Additionally, the degree of decrease in pain scores was assessed at the following time intervals: 0-15 minutes, 0-30 minutes, 0-60 minutes, and 0-120 minutes. Secondary outcomes encompassed the need for rescue analgesics and the occurrence of drug-related side effects. These data were analyzed comparatively between the two groups.

Statistical Analysis

The study data were recorded on preprepared case report forms and subsequently entered into IBM Statistics for macOs, Version 28.0 (Armonk, NY: IBM Corp) software for blind analysis. The Shapiro-Wilk test was employed to assess the normality of continuous data. Normally distributed parameters were presented as mean values, standard deviations, and 95% confidence intervals, while non-normally distributed parameters were represented as medians and interquartile ranges.

For non-normally distributed parameters, the Mann-Whitney U test was utilized to compare medians between the two groups. On the other hand, the independent samples t-test was employed to evaluate mean differences between the two groups for normally distributed parameters. The Pearson chi-square test was used to compare the ratios of categorical data between the main groups.

The data of patients whose NRS data could not be obtained were excluded from the study, and the analysis was concluded using a per-protocol analysis. A significance level of $p<0.05$ was considered for statistical significance.

Results

A total of 150 patients who met the inclusion criteria were initially enrolled in the study. However, due to 24 patients expressing a desire to withdraw from the study after enrollment, the study was completed with 126 patients via per-protocol analysis. The consort flow diagram of the study was provided as Figure 1. Of these patients, 38.1% were women, and the mean age was 42.6±13.2 years. The patients were divided into two groups: 61 (48.4%) in the 400 mg group and 65 (51.6%) in the 800 mg group. Among the participants, 75 (59.5%) had a history of urinary stones, and 44 (34.9%) had a positive family history of the condition.

The distribution of parameters, including demographic data, characteristics of symptoms (pain), urinary stone history, analgesic use, and macroscopic hematuria, among the groups, is presented in Table 1. Although there were differences in some of these parameters, none of these differences were statistically significant (Table 1).

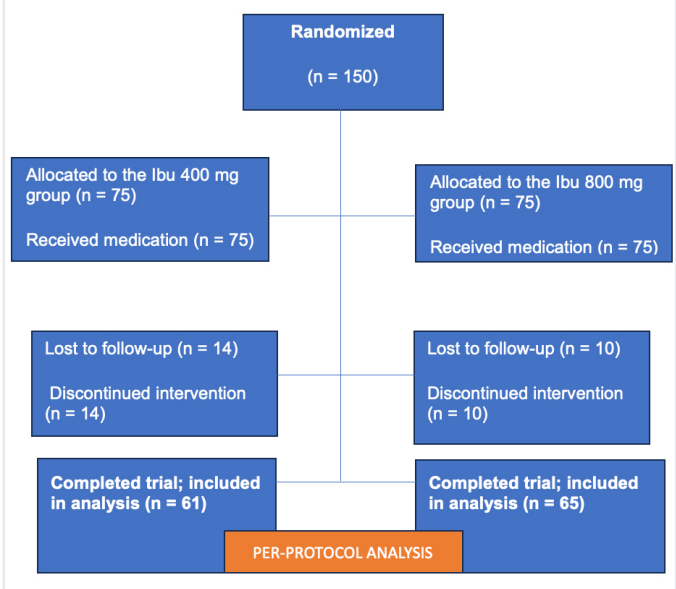

Figure 1. CONSORT flow diagram of the study

Pain measurements using the numerical rating scale at 0, 15, 30, 60, and 120 minutes, as well as the differences between these time intervals, are presented in Table 2. These parameters were compared between the two groups. In this analysis, a statistically significant difference was observed only in the "Diff 0-120" parameter. It was found that the pain score decreased more in the 800 mg group compared to the 400 mg group (Table 2, Figure 2).

Table 1. Demographic, symptom and background characteristics in 400/800 mg groups

Variables		Treatment group 400 mg			800 mg			p-value
		n (%)	Mean ± SD or median	25-75% or 95% CI	n (%)	Mean ± SD or median	25-75% or 95% CI	
Gender	Male	34 (55.7)			44 (67.7)			0.167*
	Female	27 (44.3)			21 (32.3)			
Age			42.6±12.3	39.5-45.7		42.6±14.1	39.1-46.0	0.982†
Height			168.4±9.3	166.0-171.0		169.9±7.7	168.0-172.0	0.332†
Weight			77.4±15.7	73.4-81.4		78.0±12.4	74.9-81.1	0.810†
Symptom time			13.0	4.0-22.0		16.0	5.0-48.0	0.182‡
Stone history		33 (54.1)			42 (64.6)			0.229*
Family stone history		22 (36.1)			22 (33.8)			0.794*
Pain localization	Flank	46 (75.4)			59 (90.8)			-
	Upper	6 (9.8)			3 (4.6)			
	Lower	8 (13.1)			1 (1.5)			
	Inguinal	1 (1.6)			2 (3.1)			
Pain radiation	Flank	35 (57.4)			39 (60.0)			-
	Upper	6 (9.8)			7 (10.8)			
	Lower	12 (19.7)			14 (21.5)			
	Inguinal	3 (4.9)			5 (7.7)			
	Ureter	5 (8.2)			0 (0.0)			
Agitation		17 (27.9)			21 (32.3)			0.587*
Analgesic use		12 (19.7)			14 (21.5)			0.796*
Analgesic using time			8.0	7.5-11.0		8.5	7.0-12.0	0.855‡
Stone score			8.0	6.0-9.0		7.0	6.0-8.0	0.206‡
Macroscopic haematuria		19 (31.1)			19 (29.2)			0.815*

*Pearson chi-square test, †Independent samples-t test; mean ± SD, 95% CI, ‡Mann-Whitney U test; median, interquartile range, SD: Standard deviation, CI: Confidence interval

Table 2. Numerical rating scale and differences between time periods

Variables	Treatment group 400 mg		800 mg		p-value
	Median (25-75%)	Mean ± SD	Median (25-75%)	Mean ± SD	
NRS-0	8.0 (6.0-9.0)	7.7±1.7	8.0 (7.0-9.0)	7.7±1.4	0.982
NRS-15	6.0 (4.0-7.0)	5.7±2.4	5.0 (4.0-7.0)	5.7±2.1	0.853
NRS-30	4.0 (2.0-5.0)	3.8±2.6	4.0 (2.0-5.0)	3.9±2.2	0.735
NRS-60	2.0 (0.0-4.0)	2.9±2.7	2.0 (1.0-3.0)	2.2±1.9	0.339
NRS-120	1.0 (0.0-3.0)	1.7±1.8	1.0 (0.0-2.0)	1.2±1.4	0.132
Diff0.15	2.0 (1.0-3.0)	2.0±1.7	2.0 (1.0-3.0)	2.0±1.4	0.707
Diff0.30	4.0 (3.0-5.0)	3.9±2.0	4.0 (3.0-5.0)	3.9±1.7	0.924
Diff0.60	5.0 (4.0-6.0)	4.8±2.1	6.0 (5.0-7.0)	5.5±1.5	0.050
Diff0.120	6.0 (5.0-7.0)	6.0±1.7	7.0 (6.0-7.0)	6.5±1.3	0.008

Mann-Whitney U test, SD: Standard deviation, NRS: Numeric rating scale

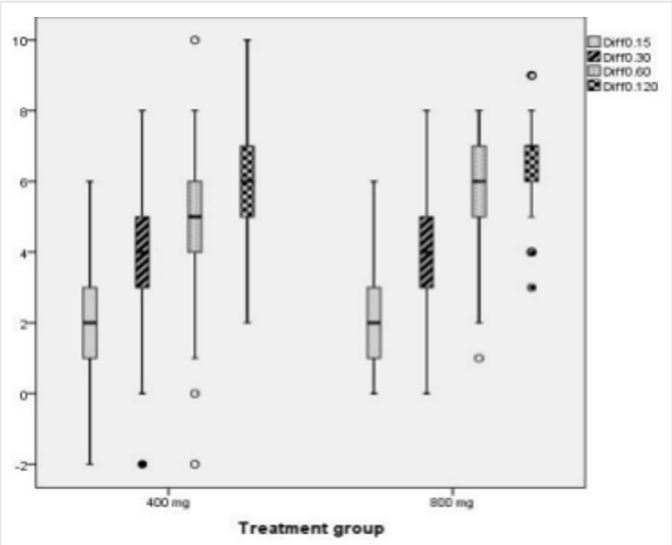

Figure 2. NRS differences in two groups
NRS: Numeric rating scale

Rescue analgesics were administered to 12 (19.7%) patients in the 400 mg group and 8 (12.3%) patients in the 800 mg group. However, this difference was not found to be statistically significant (p=0.258; Pearson chi-square test). Additionally, no drug-related side effects were observed in either group. No major or minor side effects were observed in the patients.

Discussion

The results of this study have provided us with the opportunity to compare the doses of ibuprofen and their analgesic efficacy in the treatment of patients presenting to the emergency department with suspected renal colic.

While renal colic itself is not a life-threatening condition, the pain induced by kidney stones necessitates treatment to provide comfort to the patients (9). Several factors such as male gender, advanced age, and obesity have been reported to influence the prevalence and frequency of renal colic (10). In accordance with these available data, the findings of this study exhibit similarities and concordance with the existing literature.

The pain experienced by patients suffering from renal colic demands effective analgesic treatment, and various analgesic agents, including NSAIDs, opioids, and drugs from the paracetamol group, have been employed for this purpose. Furthermore, the efficacy of the chosen analgesic plays a critical role in the treatment (11). In a clinical study comparing the intravenous (IV) forms of ibuprofen (800 mg) and paracetamol (1 gram) in the treatment of renal colic pain, it was demonstrated that the 800 mg IV ibuprofen was more effective than the 1 gram IV paracetamol (8). Another clinical study on renal colic compared the doses of 800 mg ibuprofen and 30 mg ketorolac, concluding that the ibuprofen group provided faster and more effective pain relief (9). Shaker and Borghei (12) also conducted a study with 70 patients experiencing renal colic pain, comparing 800 mg IV ibuprofen and 30 mg ketorolac. Their study showed that the change in pain scores was not statistically significant between the two groups. In another study conducted by Safaie et al. (13), it was demonstrated that combinations of ibuprofen (800 mg) with morphine (5 mg) and ketorolac (30 mg) with morphine (5 mg) were more effective than morphine alone, and both combinations exhibited similar efficacy. These findings suggest that ibuprofen either provides faster and more effective pain control than other analgesics or enhances the analgesic efficacy when used in combination treatments.

This current study supports the notion that the 800 mg form of ibuprofen is more effective. In previous studies related to renal colic, the 800 mg dose of ibuprofen has been considered an effective dose, and successful results have been obtained (11-13). There are also studies in the literature that investigate different doses of ibuprofen for the same conditions. For instance, in a study conducted with patients suffering from migraine-type headaches, both 200 mg and 400 mg IV doses of ibuprofen were found to be superior to placebo and exhibited similar efficacy (14). In a placebo-controlled study aimed at postoperative pain control, both 400 mg and 800 mg IV doses of ibuprofen were found to be significantly effective compared to placebo and had similar efficacy (15). When examining the time curve of this study, it became evident that the 800 mg dose of ibuprofen provided more effective pain relief in the second hour. Although the results of this study and other studies in the literature may differ across disease groups, it is suggested that the pain relief property of ibuprofen yields more efficient results with increasing doses. A review by Derry et al. (16) reported a parallel relationship between the use of ibuprofen at increasing doses in the treatment of post-dental operation pain control, with increased effectiveness as the dose increased.

Additionally, in a meta-analysis conducted on renal colic cases, it was reported that ibuprofen and ketorolac exhibited similar analgesic efficacy up to the 120th minute (17). Furthermore, in a study conducted by Özdemir et al. (18), where they compared paracetamol, ibuprofen, and dexketoprofen, they compared all three drug groups and reported no statistically significant differences among them. In the same study, they also compared the 400 mg and 800 mg doses of ibuprofen and found no statistical difference between them. Therefore, the presence of a statistical difference in favor of the 800 mg dose of ibuprofen in our results does not align with the literature.

In conclusion, the superior or similar efficacy of ibuprofen observed in studies involving different drug groups has prompted the need for a dose comparison evaluation of ibuprofen. This study, considering the number of patients, demographic data, patient height and weight ratios, NRS and stone scoring, demonstrated that the groups were homogeneously distributed. This homogeneous and balanced distribution of the groups enhanced the reliability of the study. Although the NRS difference values were similar up to the 60th minute, the difference became more significant in the group using 800 mg of ibuprofen at the 120th minute. Additionally, the lower requirement for rescue medication and the absence of a difference between the two

groups in terms of side effects suggest that 800 mg of ibuprofen is a more preferable option for controlling renal colic pain.

Study Limitation

The use of the NRS for pain grading, while advantageous for its ease of use, may not provide as sensitive results as the visual analog scale. Not monitoring pain beyond the 120th minute can also be considered a separate limitation of this study. Furthermore, not conducting the study with a larger sample size is among the limitations of the study. The absence of other treatment doses also represents another limitation. Given that emergency departments are environments characterized by rapid patient turnover and circulation, the inability to monitor patients for longer periods, even for study purposes, can be considered a significant limitation and weakness. Since the study concluded at the 120th minute, it is unknown whether patients experienced recurrent pain within the 24-hour timeframe or required additional medical treatment. However, future studies can be designed considering these factors.

Conclusion

Based on the findings of this study, it can be concluded that the IV formulation of ibuprofen at a dose of 800 mg has more effective analgesic activity in the treatment of renal colic. Therefore, it may be more rational to use the 800 mg IV dose of ibuprofen, especially since there were no serious side effects associated with its use. Given the widespread use of ibuprofen in this context, it is likely that these results can be readily applied in clinical practice.

Ethics

Ethics Committee Approval: Approval was obtained from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (decision number: 2, date: 27.10.2022).

Informed Consent: All patients participating in the study were informed, and written informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.F., E.T., A.B.E., A.Ş., Concept: S.F., E.T., A.B.E., A.Ş., Design: S.F., E.T., A.B.E., A.Ş., Data Collection or Processing: S.F., A.B.E., A.Ş., M.Y., E.Ü., Analysis or Interpretation: S.F., A.Ş., Literature Search: S.F., E.T., A.B.E., A.Ş., M.Y., E.Ü., Writing: S.F., E.T., A.B.E., A.Ş., M.Y., E.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

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