Original Article

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Analgesic Efficacy of Ibuprofen in Dysmenorrhea

Dismenorede İbuprofen'in Analjezik Etkinliği

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ABSTRACT

Objective: Non-steroidal anti-inflammatory drugs (NSAIDs) are used routinely and as first choice in the analgesic treatment of abdominal pain caused by primary dysmenorrhea (PD). In our study, we aimed to compare the analgesic efficacy of 400 mg and 800 mg ibuprofen doses administered intravenously (iv) in the treatment of patients presenting with abdominal pain due to PD.

Methods: The study was conducted in emergency department over a period of 4 months in a prospective, randomized, controlled and single-blind design. Females aged between 18-50 years were included in the study. The patients were randomly divided into two groups as those who received ibuprofen 400 mg and those who received 800 mg. In these two groups, the pain scores of the patients at 0, 30 and 60 min were determined and analyzed using the 10-unit Numeric Rating Scale (NRS).

Results: A total of 54 patients, 27 in each group were included in the study. Age, weight and body mass index parameters of the groups were statistically similar. There was no statistically significant difference between the two groups in terms of the degree of pain at admission and at the 30th-60th min of follow-up. In the 400 mg and 800 mg treatment groups, the NRS score differences between 0 and30 min periods [median [interquartile range (IQR): 4 (3-5) and 4 (3-4); p=0.224] and between 0 and 60 min periods [median (IQR): 4 (3-5) and 4 (3-4); p=0.224] were statistically similar. There was no difference between the two groups in terms of need for rescue medication and side effects.

Conclusion: Similar efficacy is observed in reducing pain intensity between 400 mg and 800 mg doses of iv ibuprofen. According to these findings, it can be concluded that 400 mg of ibuprofen

ÖZ

Amaç: Non-steroid anti-enflamatuvar ilaçlar (NSAİİ) primer dismenorenin (PD) neden olduğu karın ağrısının tedavisinde rutinde ilk tercih olarak kullanılmaktadır. Çalışmamızda PD nedeniyle karın ağrısı ile başvuran hastaların tedavisinde intravenöz (i.v.) olarak uygulanan 400 mg ve 800 mg ibuprofen dozlarının analjezik etkinliğini karşılaştırmayı amaçladık.

Yöntemler: Çalışma acil serviste, ileriye dönük, randomize, kontrollü ve tek kör tasarım ile 4 aylık bir süre boyunca yürütüldü. Çalışmaya 18-50 yaş arası kadınlar dahil edildi. Hastalar randomize olarak uygulanan ibuprofen dozuna göre 400 mg ve 800 mg i.v. olmak üzere iki gruba ayrıldı. Bu iki gruptaki hastaların 0, 30 ve 60 dakikadaki ağrı skorları belirlendi ve Numerik Rating Skala (NRS) kullanılarak analiz edildi.

Bulgular: Her grupta 27 olmak üzere toplam 54 hasta çalışmaya dahil edildi. Grupların yaş, kilo ve vücut kitle indeksi parametreleri arasında istatistiksel olarak fark yoktu. İki grup arasında başvurudaki ve 30-60. dakikalardaki ağrı dereceleri açısından istatistiksel olarak anlamlı fark yoktu. Dört yüz mg ve 800 mg tedavi gruplarında, hem 0-30 dakikalık dönem NRS farklılıkları [medyan (IQR): 4 (3-5) ve 4 (3-4); p=0,224] hem de 0-60 dakikalık dönem NRS farklılıkları [medyan (IQR): 4 [3-5] ve 4 (3-4); p=0,224] istatistiksel olarak benzerdi. Kurtarma ilacı ihtiyacı ve yan etkiler açısından iki grup arasında fark yoktu.

Sonuç: Ağrı yoğunluğunu azaltmada 400 mg ve 800 mg i.v. ibuprofen dozlarının etkinliklerinin benzer olduğu gözlendi. Bu bulgulara göre PD'li hastalarda karın ağrısı tedavisinde 400 mg ibuprofen i.v. preparatının 800 mg yerine tercih edilebileceği söylenebilir.

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ABSTRACT

IV preparation can be preferred over 800 mg in the treatment of abdominal pain in patients with PD.

Keywords: Abdominal pain, ibuprofen, intravenous, Numeric Rating Scale, primary dysmenorrhea

ÖZ

Anahtar Sözcükler: Karın ağrısı, ibuprofen, intravenöz, Numerik Rating Skala, primer dismenore

Introduction

Dysmenorrhea is a gynecological problem accompanied by painful cramps during menstruation. It affects more than 50% of women during the menstrual period. In addition, there are publications stating that it affects more than 90% of women between the ages of 18-45 (1). In addition, it is known that abdominal pain due to dysmenorrhea is a serious burden in emergency services. Dysmenorrhea is classified as primary and secondary. Primary dysmenorrhea (PD) is a type of dysmenorrhea that occurs without underlying pelvic pathology. It is known that the strong vasoconstrictive and myometrium stimulating effect of prostaglandin-F2 alpha is responsible for the current pathogenesis of PD. NSAIDs suppress the activity of the cyclooxygenase-2 (COX-2) enzyme, thereby reducing cyclic endoperoxide production and prostaglandin levels, contributing to patients' analgesia and comfort (2). Based on these mechanisms, NSAIDs have gained a wide place in the treatment of PD, and it is known that NSAIDs are the preferred drug group in dysmenorrhea complaints (3).

The primary mechanism of action of ibuprofen from the NSAID drug group is through the inhibition of prostaglandin precursors. After physiological and pathological stimulation, membrane phospholipids secrete arachidonic acid in conjunction with the phospholipase A2 enzyme. Arachidonic acid then switches to one of three different enzymatic pathways: cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP450) (4). The COX route is an important factor for the current stated uses of ibuprofen. There are three different isoforms in the COX pathway: COX-1 (PGH synthase), COX-2 and COX-3. Inhibition of the COX-1 and COX-2 pathways reduces the release of prostaglandin precursors, which in turn reduces the severity of the cellular response to pathological and physiological stimuli. Non-selective NSAIDs such as ibuprofen show their analgesic properties by this mechanism (5).

The 400 mg and 800 mg intravenous (IV) forms of ibuprofen are approved for use in PD. However, no study was found comparing the analgesic efficacy of 400 mg and 800 mg IV doses of ibuprofen. The aim of this study was to compare the analgesic efficacy of 400 and 800 mg IV doses of ibuprofen in the control of moderate and severe pain in PD.

Methods

Settings and Design

This study was conducted in the Emergency Clinic of Ankara Bilkent City Hospital between 01.05.2021 and 31.08.2021 according to a prospective, randomized, controlled and single-blind research model. Approval for the study was obtained from the Clinical Research Ethics Committee of Ankara Bilkent City Hospital (date/number: 14.04.2021/E1-21-1609). Informed consent was obtained from all patients.

Participants and Definitions

Patients who suffered from recurrent abdominal pain occurring during the menstrual cycle, with a diagnosis of PD were included in the study. Those who were hemodynamically stable and who volunteered to participate in the study were included. Other inclusion criteria were; patients with regular menstrual cycles with current pain "similar to pain in previous cycles", between the ages of 18-50, at pain score of baseline Numeric Rating Scale (NRS) ≥5. Exclusion criteria were; patients who were suspected or diagnosed with acute medical/surgical illness or pregnancy. Other exclusion criteria were: drug allergy to the subject of the study, and contraindications for the use of ibuprofen (such as acute renal failure, recent bypass surgery, liver failure, etc.), patients who used any analgesic drug in the last 6 hours. Mentally retarded or uncooperative subjects with hearing and/or visual impairments or any underlying organic neurological disorders were also excluded from the study. The population of the study consisted of female patients who presented to the emergency department with the complaint of "abdominal pain during the menstrual cycle", and the sample sample consisted of patients who met the criteria for participation in the research in the specified population. The pain scoring system utilized was NRS (Numeric Rating Scale), which is a numerically graded visual analog scale. This 11-point numerical scale ranges from "0" representing "no pain" to "10" representing "worst pain imaginable" (Figure 1). Body-mass index was calculated using the weight and height values of the patients (weight/height squared; kg/m^2) and added to the analysis.

Intervention

The patient who met the inclusion criteria of our study was taken to a reserved examination room. Detailed information about the drugs used in the study along with the list of drugs that can be administered to the patients was given to the patients by the doctor there, and an informed consent form was signed. The initial pain score before the procedure was determined and recorded using the 10-unit NRS. NRS markings on the case report forms were made by the patient before and during the procedure, regardless of the previous marking. The patient's file numbers, height, weight, age, gender, application date and time were recorded along with the drug number applied on the same form. Oxygen saturation, blood pressure, rhythm

Figure 1. Numeric rating scale

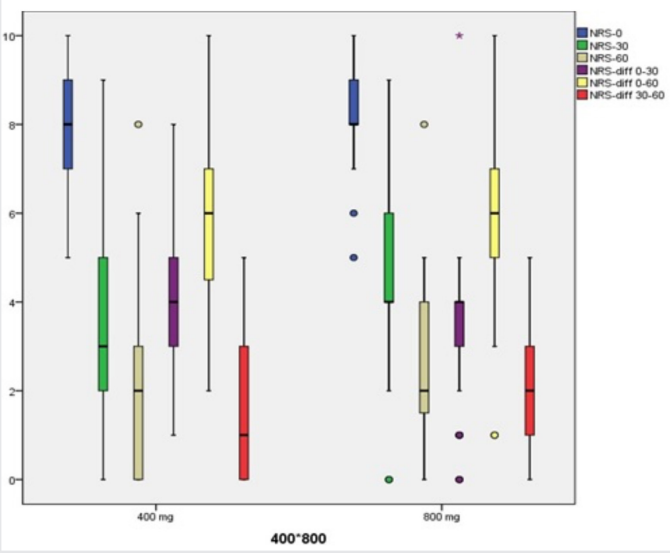

Figure 2. NRS scores and differences in two groups
NRS: Numeric Rating Scale

and body temperature were monitored during the procedure. NRS scores at 30 and 60 minutes after randomization were evaluated and recorded. Rescue treatment protocol was started for patients whose pain score did not decrease or increased at 30 minutes, or whose NRS score was >3 at 60 minutes. As salvage treatment, tramadol hydrochloride was planned as 100 mg IV as a 30-minute infusion in 500 mL physiological saline.

Randomization was carried out using the closed envelope method. Group names of 400 mg and 800 mg were written in a total of 54 sealed envelopes, 27 for each group. The baseline NRS score was determined for patients who met the criteria and were accepted into the study, and randomization was performed for patients with this value ≥5. For this purpose, 1 sealed envelope was randomly selected and administered to the patient in 150 mL of 0.9% NaCl IV ibuprofen at the dose written in it for 10 minutes. At this stage, only the patient was blinded to the drug group. Researchers and other healthcare professionals were not blinded to the practice.

Outcomes

As a result, in the case report forms, age, gender, presence of chronic disease, vital signs, admission complaint, onset time of the complaint, pain localization, pain spread, previous analgesic use, if used, when, the treatment given, at 0, 30 and 60 minutes. NRS pain score, whether or not rescue medication was used and whether there were any side effects were recorded. These data were analyzed comparatively between the two groups, considering the pain scores at 30-60 minutes and the degree of pain score reduction in the 0-30 and 0-60 minute periods as primary outcomes, the need for rescue analgesics and drug side effects as secondary outcomes.

Statistical Analysis

IBM SPSS.16 for Windows (SPSS Inc., Chicago, Ill., USA) program was used for statistical analysis of the study. In the study, Pearson chi-square and Fisher's Exact tests were used for ratio comparisons of categorical data. Distribution analysis of continuous data was made with the Shapiro-Wilk test, comparisons of medians between two groups of non-normally distributed data were made with Mann-Whitney U test, and mean comparisons between two independent groups in data with normal distribution were made with Independent Samples t-test. Statistical significance was generally used at the $p<0.05$ level.

For the study, a sample size analysis was carried out using the data in the study of Ayan et al. (6). In this analysis, it was calculated that at least 26 patients should be included in each group based on the initial VAS score standard deviation of 16 mm, 95% power, and 5% Type 1 error.

Results

A total of 54 female patients were included in the study, 27 patients (50%) in both groups (400 mg and 800 mg). No patients were excluded from the study after randomization, and all patients received the planned treatment and follow-up. Analyzes were performed on 54 (100%) patients. The age distribution of the patients in the two groups was similar (median: 25 vs 24; p=0.521). Weight, body mass index, family history, pain onset time, and previous analgesic use were also found to be homogeneously distributed in both groups (Table 1). Quadrants where abdominal pain is localized are also shown in Table 1. In the patient histories, it was determined that pain was observed regularly in every cycle in 47 (87.0%) of the patients.

The degree of pain at admission (NRS-0) and 30-60 at follow-up. There was no statistically significant difference between the two groups in terms of pain degree (NRS-30 and NRS-60) in minutes (Table 2). Although the mean of NRS-30 was higher in the "800 mg" group (mean ± standard deviation [95% confidence interval: 4.7±2.2 (3.8-5.5) vs 3.6±2.6 (2.6) -4.6); p=0.114], this difference was not statistically significant (Table 2). Figure 2 shows the box-plot graph of these three pain levels.

Table 1. Demographics and clinical features

Parameters		Ibuprofen dose 400 mg n=27 (50%) Median (IQR)	800 mg n=27 (50%) Median (IQR)	p-value
Age (year)		25 (22-28)	24 (21-27)	0.521*
Weight (kg)		52 (50-60)	56 (53-60)	0.327*
BMI		21.56 (19.48-23.31)	20,45 (19.57-21.01)	0.411*
Dose for per kg		7.69 (6.67-8)	14,29 (13.33-15.09)	<0,001*
First menstrual cycle (day)		13 (13-14)	14 (14-14)	0.028*
Complaint time (hour)		5 (2-10)	6 (3-8)	0.917*
Family history- **n (%)**		6 (33.3)	11 (61.1)	0.095†
Pain in all cycle- **n (%)**		21 (77.8)	26 (96.3)	0.100‡
Pain quadrant **n (%)**	Diffuse	1 (3.7)	4 (14.8)	-
	Suprapubic	21 (77.8)	19 (70.4)	
	Right lower	2 (7.4)	1 (3.7)	
	Left lower	3 (11.1)	3 (11.1)	
Agitation- **n (%)**		8 (29.6)	17 (63.0)	0.014†
Prior analgesia- **n (%)**		1 (3.7)	5 (18.5)	0.192‡
Prior analgesia (hours ago)		24 (24-24)	8 (8-8)	0.206*

*Mann-Whitney U test
†Pearson chi-squared test
‡Fisher's Exact test
IQR: Interquartile range, BMI: Body mass index

Table 2. NRS and other main outcomes

Parameters	Ibuprofen dose 400 mg Median (IQR)	800 mg Median (IQR)	p-value
NRS0	8 (7-9)	8 (8-9)	0.224*
NRS30- **mean ± SD (95% CI)**	3.6±2.6 (2.6-4.6)	4.7±2.2 (3.8-5.5)	0.114†
NRS60	2 (0-3)	2 (1-4)	0.310*
Rescue medicine- **n (%)**	2 (7.4)	1 (3.7)	1.000‡
Side effect- **n (%)**	1 (3.7)	0 (0)	1.000‡

*Mann-Whitney U test
†Independent Samples t-test- mean ± SD (95% confidence interval)
‡Fisher's Exact test
IQR: Interquartile range, NRS0: Initial Numeric Rating Scale, NRS30: Numeric Rating Scale (30th minute), NRS60: Numeric Rating Scale (60th minute)

Table 3. Difference in NRS (30th and 60th minutes)

Parameters	Ibuprofen dose 400 mg	800 mg	p-value
NRS-diff 0-30, **median (IQR)**	4 (3-5)	4 (3-4)	0.224*
NRS-diff 0-60, **mean ± SD (95% CI)**	5.8±1.8 (2.6-4.6)	5.8±2.2 (3.8-5.5)	0.114†
NRS-diff 30-60, **median (IQR)**	1 (0-3)	2 (1-3)	0.137*

*Mann-Whitney U test
†Independent Samples t-test- mean ± SD (95% confidence interval)
NRS: Numeric Rating Scale, NRS-diff: NRS difference, IQR: Interquartile range, SD: Standard deviation, CI: Confidence interval

The need for rescue medication was seen in 3 patients in all patients, the rate here being 7.4% in the first group and 3.7% in the second group (p=1,000). Adverse effects were detected as "nausea-vomiting" in only 1 patient (3.7%) in the 400 mg group (Table 2).

In addition, changes in the degree of pain were also analyzed. Differences in NRS at 0-30 minutes were similar between the 400 mg and 800 mg groups [median (IQR): 4 (3-5) vs 4 (3-4); p=224], respectively. Similarly, the NRS differences between 0-60 minutes [respectively, median (IQR): 5.8±1.8 (2.6-4.6) vs. 5.8±2.2 (3.8-5.5); p=114] were also found to be similar. Although the median of the 30-60 minute difference in the 800 mg" group was high [median (IQR): 1 (0-3) vs 2 (1-3); p=137], this difference was not statistically significant (Table 3). These differences are also expressed graphically (Figure 2).

Discussion

Dysmenorrhea is a common gynecological problem consisting of painful cramps accompanying menstruation and is classified as PD when there is no underlying abnormality. Studies have shown that women with dysmenorrhea have high levels of prostaglandins, which play a role in the etiology of pain. NSAIDs provide analgesic effects by suppressing prostaglandin synthesis (7). In this study, the analgesic efficacy of 400 mg and 800 mg IV doses of ibuprofen, which is a drug from the NSAID group, which is frequently used in dysmenorrhea, was found to be similar. As far as we could detect from the literature, this study is the first to compare the effectiveness of different doses of ibuprofen in dysmenorrhea pain.

The prospective and randomized design of the study is one of its strengths, and the fact that the participants are blind to drug doses is another factor that increases reliability. However, the fact that researchers and healthcare personnel are not blind should be considered a handicap, on the contrary. Since there is no data on the characteristics of the participants such as whether they are virgins, previous sexual activities, gravida-parity and presence of intrauterine device, the results of the study cannot be customized to any patient group related to these conditions.

It has been proven that various factors such as early menarche age, increased menstrual bleeding, alcohol and tobacco use, low socioeconomic status, obesity, depression, nulliparity, irregular menstrual cycle, long menstruation duration, and family history of dysmenorrhea increase the risk of dysmenorrhea (8-10). First of all, the age at which the patients included in the study at first menstruation and menstruation with regular cycles were consistent with the literature. There was a family history of dysmenorrhea in 17 of our patients. Although this is an important risk factor for dysmonea, it was seen at a rate similar to other studies (10). In this study, the median body-mass index was 20.56 (19.53-22.31); Similar values are also mentioned in the study of Camlibel et al. (2) conditions seen in women during the menstrual cycle include mood disorders such as anxiety, depression, irritability and irritability (10). Agitation and anxiety were present in 46.3% of the patients included in our study. Although the relationship between anxiety and pain has been evaluated in different diseases, this subject is open to study in dysmenorrhea cases. Studies have also shown that women younger than 25 are more likely to have PD, and its prevalence decreases with increasing age (10). In our study, the mean age of the patients was calculated similar to the existing data for both groups. In the literature, it has been reported that pain levels are moderate and severe in the significant majority of PD patients (11-13). In the results we found in our study, the pain levels of the patients at the time of admission were moderate to high.

Although the pathophysiology of PD is not fully clarified, it is thought that increased prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) levels in the etiology increase the sensitivity of myometrial contractions, uterine ischemia and pain fibers (9,14,15). For this reason, NSAIDs act as a building block in the treatment of PD, as they suppress prostaglandin synthesis by inhibition of COX enzyme, and ibuprofen and many other NSAIDs are primarily preferred among treatment options (14,16).

There are many studies with ibuprofen in the treatment of PD. However, most of these studies are studies comparing ibuprofen versus another agent. In a study, ibuprofen's 400 mg form versus placebo and 64 mg doses of proxifen were compared, and it was stated that the analgesic efficacy of ibuprofen was superior (17). In another study in which 33 patients were evaluated for 3 months, it was shown that ibuprofen was superior to the other two agents in the treatment of ibuprofen 200 mg, aspirin 425 mg and placebo (13). In another study involving 55 female patients, it was shown that the analgesic efficacy of ibuprofen 400 mg dose was superior to proxifen hydrochloride and placebo (18).

In a study conducted in Spain, it was reported that women with dysmenorrhea used analgesics such as NSAIDs, paracetamol, and antispasmodics due to existing pain, and most of them used mefenamic acid, ibuprofen, paracetamol, ketoprofen, and diclofenac (19). In addition, in another study, it was seen that the primary preferences of most of the patients were ibuprofen and diclofenac (20) Although all these analgesic drugs used in the treatment of dysmenorrhea were effective in reducing the degree of pain regardless of the frequency of use, dose range and administration route, ketoprofen and other NSAIDs were more effective than paracetamol, but there was no statistically significant difference between NSAIDs (10).

Ibuprofen and naproxen, which are arylpropionic acid derivatives, are frequently preferred in the treatment of dysmenorrhea and have less side-effect profiles than other NSAIDs. It has been shown that 80% of patients treated with ibuprofen and naproxen provide almost perfect relief compared to placebo (21). Zhang et al. (22) as a result of scanning 56 studies in dysmenorrhea; It was stated that ibuprofen, naproxen, aspirin and mefenamic acid were superior to placebo. In addition, it has been shown that naproxen and ibuprofen have less need for rescue medication, less restriction of daily life, and adaptation problems to work or school life, and that the side-effect profile of ibuprofen has a lower side-effect profile (22). In a meta-analysis to evaluate the

efficacy and safety of naproxen, ibuprofen, diclofenac, aspirin, and ketoprofen, it was stated that diclofenac and ibuprofen were more effective than others in their analgesic efficacy in PD, and ketoprofen and ibuprofen were the safest agents in the safety evaluation (23). In line with the current studies and meta-analyses, ibuprofen stands out among other NSAIDs in terms of its effectiveness and safety.

Comparing the analgesic efficacy of ibuprofen 400 and 800 mg in the treatment of postoperative pain, 800 mg of ibuprofen was used in orthopedic trauma patients, 800 mg of ibuprofen was used after hip replacement surgery, and ibuprofen 800 mg iv. There are studies in the literature in which the effectiveness of the form is superior (24-26). A study comparing the analgesic efficacy of 400 and 800 mg doses of ibuprofen in studies with PD could not be found in the literature. According to the information in the prospectus, it is recommended to use the parenteral form of ibuprofen at a dose of 200-400 mg for antipyretic purposes, and 400-800 mg as an analgesic. In this study, 400-800 mg doses of ibuprofen were selected for moderate-to-severe pain pattern. The degrees of NRS reduction were found to be similar in the 0-30 and 0-60 minute periods of their analgesic effects; with these data, it can be thought that the 400 mg dose should be chosen as a priority. It is recommended that these doses be repeated every 4-6 hours. In this study, there is no data on the processes after the 60th minute due to the short follow-up times in the emergency department. However, since this study was conducted in the group of patients who applied to the emergency department, the importance of the first hour in pain treatment seems obvious in these conditions. Maintenance oral treatments that will be offered to the patient at discharge may help achieve analgesia goals within days; however, these goals are not the subject of this study.

Study Limitations

The most important limitation of the study is that the researchers were not blinded in the study design. In addition, although the number of cases was determined according to the sample size analysis, more reliable results can be obtained with higher patient numbers. NRS score was used for pain grading due to the advantage of easy use, and we can say that more sensitive results can be obtained with the visual analog scale. The fact that the pain was not followed up from the 60th minute can be counted as a separate limitation.

Conclusion

According to the results of the study, ibuprofen 400 mg and 800 mg IV forms have similar analgesic efficacy in the treatment of PD. Although no serious side effects related to ibuprofen were observed in this study, it would be more rational to use a similarly effective 400 mg IV dose. Considering that ibuprofen is used very frequently in the region where this study was conducted, we think that it will be possible to reflect these results in practice at a high rate. Comparing these doses in different indications may be important to further clarify the issue.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Clinical Research Ethics Committee of Ankara Bilkent City Hospital (date/number: 14.04.2021/E1-21-1609).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: S.D., A.Ş., A.B.E., Ç.Ç., Design: S.D., A.Ş., A.B.E., Ç.Ç., G.K.Ç., Data Collection or Processing: S.D., A.Ş., A.B.E., G.K.Ç., Analysis or Interpretation: S.D., A.Ş., G.K.Ç., Literature Search: S.D., A.Ş., A.B.E., Ç.Ç., G.K.Ç., Writing: S.D.

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