

## Comparative Effects of Naproxen, Diclofenac, and Piroxicam on Temporomandibular Disorders: A Clinical Trial

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Article Info	ABSTRACT				
<i>Article type:</i> Original Article	<b>Objectives:</b> The prevalence of temporomandibular disorders (TMDs) is increasing in adults, and they are associated with symptoms such as pain and dysfunction. Non-surgical treatment, which may include pharmacotherapy, laser therapy, and physiotherapy, is the first step in treatment of TMDs. This study aimed to compare the effects of naproxen diclofenac and piroxicam				
Article History:	on TMDs.				
Received: 22 Apr 2024 Accepted: 15 Oct 2024 Published: 05 May 2025	<b>Materials and Methods:</b> This clinical trial was conducted on 104 patien who were randomly assigned to four groups (n=26) to receive either 500m naproxen tablets, 50mg diclofenac tablets, 10mg piroxicam capsules, or the placebo. The patients were evaluated for pain, clicking, tenderness, ar				
* <b>Corresponding author:</b> Private practice, Imam Hossein BLV, Koshkuiyeh district, Rafsanjan, Kerman, Iran	maximum mouth opening (MMO) in five stages, i.e., before starting the treatment and 1 week, 3 weeks, 5 weeks, and 6 weeks after starting the treatment. Data were analyzed by one-way repeated measures ANOVA with one repeated and one between-subject factor, Fisher's exact test, and Chi-square test (alpha=0.05).				
Email: <u>Dnt.s.abedini@gmail.com</u> * Corresponding author: Department of Oral and Maxillofacial Radiology, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran	<b>Results:</b> Tenderness and clicking decreased with time in all groups ( $P \le 0.05$ ). The mean pain intensity and tenderness were significantly lower in the naproxen group than the other groups ( $P < 0.05$ ).				
	<b>Conclusion:</b> Naproxen tablets can reduce pain and tenderness in TMD patients more than diclofenac tablets, piroxicam capsules, and the placebo.				
Email: ziahanshahiafshar@sina.tums.ac.ir	Keywords: Diclofenac; Naproxen; Piroxicam; Temporomandibular Joint Disorders				

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#### INTRODUCTION

Temporomandibular disorders (TMDs) are characterized by signs and symptoms related to the masticatory muscles, temporomandibular joint (TMJ), or both [1]. TMDs are associated with pain, tenderness, clicking, and mouth opening limitation [2]. Many etiologic factors have been proposed for TMDs including trauma, infection, osteoarthritis, immunological causes, and metabolic and neoplastic disorders [3, 4]. The American Academy of Oral and Facial Pain has divided TMDs into three subdivisions [5]: (I) TMDs due to muscle involvement, (II) TMDs

Copyright © 2025 The Authors. Published by Tehran University of Medical Sciences. This work is published as an open access article distributed under the terms of the Creative Commons Attribution 4.0 License (http://creativecommons.org/licenses/by-nc/4). Non-commercial uses of the work are permitted, provided the original work is properly cited. due to joint involvement, and (III) TMDs due to both muscle and joint involvement.

TMDs due to muscle involvement include [3] (I) Muscle spasm (strain): Tonic muscle contraction caused by the central nervous system, (II) myofascial pain and dysfunction (trigger point): A pain with muscle origin characterized by sensitive and hard muscle bands called the pain-initiating areas, (III) fibromyalgia, which is a common chronic painful musculoskeletal disorder with a wide spectrum, with 11 to 18 sensitive and painful points spread over three-fourths of the body surface, (IV) myotonic dystrophy: a dominant hereditary multisystem disorder that may affect the facial muscles in advanced disease states, and (V) myositis ossificans progressive, which is a painful and chronic diffuse inflammation and edema of the entire muscle.

TMDs due to joint involvement include the following types [3]: (I) Deviation: It is caused by real changes in the shape of the joint surfaces, including the condyle, fossa, and disc, (II) disc displacement: when the retrodiscal lamina and the collateral ligament are stretched, the upper head of the lateral pterygoid muscle causes more anterior displacement of the disc. When opening or closing, a clicking sound is heard when the disc settles in its place, (III) disc dislocation: with the return of the retrodiscal lamina and the collateral ligament, they are stretched again, and the posterior border of the disc becomes so narrow that the disc and condyle do not articulate with each other, but the disc is placed in a completely anterior position. TMDs due to both muscle and joint involvement include a combination of joint and muscle problems. The relationship between the joint components and muscles is unclear. As a general rule, the muscle part should be treated first and then the joint problems.

The main goals of TMD treatment include decreasing the joint pain, increasing the maximum mouth opening (MMO), preventing further joint damage, and improving the patient's overall quality of life. Several different treatment methods have been proposed for TMDs, which can be divided into three groups of conservative treatments, minimally invasive surgical procedures, and invasive surgical procedures [6]. Conservative methods and non-surgical therapy are the first line of treatment to reduce pain and inflammation of the muscles and joints and improve mandibular function, which consist of pharmaceutical therapy, physical therapy, laser therapy, and splint therapy [7,8].

A stabilization splint is a thin and full occlusal coverage appliance, which is made of hard acrylic resin. It has been recommended for treatment of the masticatory muscle pain. However, permanent change in occlusion is one of the potential adverse effects of splint therapy [9]. Laser therapy is effective to reduce pain but it has a small effect on improving mandibular movements in TMD patients. Well-designed studies with a large sample size are needed for further validation of this method [10].

Considering the analgesic and anti-inflammatory properties of non-steroidal anti-inflammatory drugs (NSAIDs), they are commonly used for treatment of several dental and orofacial conditions. They are the medication of choice for treatment of acute (e.g., capsulitis) and chronic (e.g., degenerative joint disease) inflammatory conditions of the joint in TMDs [11].

In patients with anatomical and articular abnormalities, surgery is recommended for treatment of TMD [12]. Surgical approaches include arthrocentesis, arthroscopy, surgical disc replacement, disc correction or removal, condylotomy, total joint replacement, and distraction osteogenesis [13].

The first step in involving patients in their treatment course is to inform them about the pathology of pain and dysfunction, the disease prognosis, and the possibility of disease progression. Usually, many of the functional problems and pain are improved or prevented to progress with conservative treatment. Changing the diet for about 6 weeks, routine indoor exercises (maximizing the amount of jaw movements, gentle stretching exercises within the range of pain tolerance through active and passive opening), and refraining from activities that may exacerbate the condition such as chewing gum, nail biting, etc. may significantly reduce the symptoms [13]. NSAIDs are highly effective to decrease pain and

inflammation through inhibition of prostaglandin synthesis [14]. NSAIDs are used as the first line of treatment for mild to moderate pain in patients with TMDs [15]. Naproxen, diclofenac, and piroxicam are three NSAIDs that are commonly used for treatment of TMDs.

Diclofenac sodium is one of the most frequently used NSAIDs for TMDs, which is prescribed in 50-mg doses twice or three times a day [16]. Naproxen (50 mg twice a day) is another NSAID with a proven analgesic efficacy for TMDs compared with the placebo and celecoxib [17]. A previous study indicated that 20 mg piroxicam had greater analgesic efficacy over 10 days in reducing TMJ pain, compared to low-level laser therapy, at the 30day follow-up [18].

Moreover, topical application of diclofenac in the form of cream or ointment over the TMJ caused fast relief of masticatory muscle pain as monotherapy and also in combination with acetaminophen, carisoprodol, and caffeine compared with the placebo [19]. To the best of the authors' knowledge, no previous study has compared the efficacy of naproxen, diclofenac, and piroxicam in equal circumstances. Thus, this study aimed to compare the efficacy of naproxen, diclofenac, and piroxicam in comparison with a placebo for treatment of TMDs to find the best medication for treatment of patients with TMDs.

#### **MATERIALS AND METHODS**

This randomized, triple-blind clinical trial initially selected 109 TMD patients aged 20-45 years presenting to Kerman Faculty of Dentistry. However, one patient did not meet the inclusion criterion of daily pain in masticatory muscles and was excluded. Additionally, three patients were excluded due to prior laser treatment for TMD disorder, and one due to previous pharmaceutical therapy. The ethics committee of Rafsanjan University of Medical Sciences approved this study with the ethical code 139487. It was also registered in the Iranian Registry of Clinical Trials (IRCT registration number: IRCT20210807052101N1). Written informed consent was obtained from all patients. Sample size calculation:

The sample size was calculated according to a

previous study [17] assuming alpha=0.05 and beta=0.2, using the sample size calculation formula as follows:

$$n = \frac{2\sigma_d^2 \left( Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2}{\delta^2}$$
  
 $\alpha = 0.05 \rightarrow Z_{1-\frac{\alpha}{2}} = 1.96$   
 $\beta = 0.20 \rightarrow Z_{1-\beta} = 0.85$   
 $\sigma_d = 6.39, \delta = 5$ 

 $n_{\text{Naproxen}} = n_{\text{Diclofenac}} = n_{\text{Piroxicam}} = n_{\text{Placebo}} \approx 26$ 

### Eligibility criteria:

The inclusion criteria were daily pain in the masticatory muscles, limited jaw movement and clicking sound, and TMJ pain on palpation [20, 21].

The exclusion criteria were history of previous supportive treatments like physiotherapy and pharmacotherapy and systematic diseases [22]. Interventions:

The patients were instructed to consume soft foods and limit opening and closing their mouth [13]. Then, the patients (n=104) were randomly divided into four groups (n=26) by using a table of random numbers to be treated with either naproxen tablets, diclofenac tablets, piroxicam capsules, or the placebo in the form of capsules [23].

In the first group, 500 mg naproxen tablets (Chemidarou, Tehran, Iran) were prescribed twice a day for 10 days [24]. In the second group, 50mg diclofenac tablets (Shahredaru, Tehran, Iran) were prescribed twice a day for 10 days [25]. In the third group, 10mg piroxicam capsules (Zahravi, Tehran, Iran) were prescribed twice a day for 10 days. In the fourth group, placebo capsules containing starch were prescribed twice a day for 10 days [23]. The patients were unaware of the medication type they received. Prescription of the placebo was done according to previous studies by Singer and Dionne [23], Jagger [26], Ekberg et al, [27] and Varoli et al [19].

A visual analog scale (VAS) was used to quantify the pain level of the patients, which was scored from 0 to 10 (0=no pain and 10=maximum pain), and was provided to them on every session.

Presence of clicking in the TMJ was determined

by a stethoscope and palpation of the region in front of the ear orifice while opening and closing the mouth [28]. To examine the MMO in the active manner [active range of motion (AROM)], a fabric millimeter-scale ruler was used to measure the vertical distance between the upper and lower incisors in each session [28]. To assess the tenderness, the TMJ area and the temporalis and masseter muscles were palpated in each session [1]. The timetable for evaluation of patients included a first assessment before starting the treatment, a second assessment one week after the treatment, a third assessment 3 weeks after the treatment, a fourth assessment 5 weeks after the treatment, and a fifth assessment 6 weeks after the treatment [23]. The examiner who evaluated the patients in the examination sessions and the statistician were both blinded to the group allocation of the patients.

Data were analyzed by SPSS version 18 (SPSS Inc., Chicago, IL, USA). Quantitative variables were reported as mean  $\pm$  standard deviation, and qualitative variables were presented as

number and percentage. One-way repeated measures ANOVA with one repeated and one between-subject factor was used to assess the trend of change in the VAS pain score and AROM at the scheduled time points (before starting the treatment and 1 week, 3 weeks, 5 weeks, and 6 weeks after starting the treatment) across the treatment groups. Oneway ANOVA was sued to compare the baseline characteristics among the four groups. Furthermore, the Chi-square test and Fisher's exact test were used to compare tenderness and clicking frequency among the treatment groups. The significance level was set at 0.05.

#### RESULTS

A total of 109 patients were initially assessed, but five were excluded (one did not meet the inclusion criterion, and four met the exclusion criteria). The remaining 104 eligible participants were randomly assigned to four groups (26 per group). No participants were lost to follow-up, and all completed the study (Fig 1).



#### Fig 1. CONSORT flow diagram of patient selection and allocation

As shown in Table 1, one-way ANOVA indicated no statistically significant difference in the mean age, pain intensity, and MMO among the studv groups (P>0.05). Furthermore, the Chi-square test showed no statistically significant difference in the frequency distribution of gender and tenderness among the study groups (P>0.05). The Fisher's exact test revealed no statistically significant difference in the frequency distribution of clicking among the treatment groups (P>0.05).

According to Figure 2, one-way repeated measures ANOVA with one repeated and one between-subject factor indicated the significant effect of group on the VAS pain score (F=18.464, df=3, P<0.001). In other words, regardless of the time point, there was a statistically significant difference among the groups in the VAS pain score. One-way ANOVA showed that the mean pain score was significantly lower in the naproxen group than in the placebo group in the first week (P=0.027), third week (P<0.001), fifth week (P=0.026), and sixth week (P=0.019), and there was no statistically significant difference between the mean values of other groups (P>0.05). Moreover, the effect of time on the VAS pain score was statistically significant (F=60.905, df=4, P<0.001). On the other hand, regardless of the group, the VAS pain score decreased during the study period. Furthermore, the interaction effect of time and study group was not statistically significant on the VAS pain score (P=0.768, df=12, F=0.684), i.e. there was no statistically significant difference in the pain reduction rate during the study period across the four groups.

According to Figure 3, one-way repeated measures ANOVA with one repeated and one between-subject factor indicated that the effect of group was not significant on MMO (F=0.590, df=3, P=0.622). It means that regardless of the time point, the difference among the groups was not statistically significant regarding MMO. The effect of time on MMO was not statistically significant either (P=0.251, df=4, F=1.347). It means that regardless of the study group, there was no significant change in the MMO during the study period.

The interaction effect of time and group was not statistically significant on MMO (P=0.997, df=12, F=0.223). It means that the slope (speed) of increasing the MMO in the study groups during the study period was not significantly different. In other words, there was no significant difference in MMO among the study groups.

As shown in Table 2, the Chi-square test and Fisher's exact test indicated no statistically significant difference in the frequency distribution of clicking at any time point among the study groups. Moreover, the Chi-square test and Fisher's exact test showed a statistically significant difference in the distribution of tenderness in the third, fifth, and sixth weeks among the study groups, as the distribution of tenderness was significantly lower in the naproxen group than in the placebo group (P=0.049, P=0.030, and P=0.011, respectively). The results also indicated that tenderness and clicking decreased in all groups over time (P<0.05).

Variable		Naproxen (n=26)	Diclofenac (n=26)	Piroxicam (n=26)	Placebo (n=26)	P-value
Age (yrs.)		28.81±5.39	29.15±5.16	29.38±5.43	27.85±5.10	0.732
Gender	Male	10 (38.5)	11 (42.3)	11 (42.3)	12 (46.2)	0.957
	Female	16 (61.5)	15 (57.7)	15 (57.7)	14 (53.8)	
VAS pain score		4.69±3.34	5.23±3.05	4.92±3.16	5.54±3.01	0.784
AROM (mr	n)	37.69±7.01	39.27±8.08	39.92±6.64	39.54±6.57	0.632
Clicking		22 (84.6)	24 (92.3)	24 (92.3)	23 (88.5)	0.898
Tenderness		18 (69.2)	20 (76.9)	19 (73.1)	21 (80.8)	0.795

**Table 1.** Comparison of the study variables among the treatment groups before the TMD treatment

Data are expressed as mean ± standard deviation or as number (%).



Fig 2. Comparison of the trend of change in the mean VAS pain score in each treatment group

Fig 3. Comparison of the trend of change in the mean AROM in the study groups

Table 2. Com	parison of the	requency of	f clicking and	d tenderness in	the study groups
	parison or the	requeries of	i chenng and	a tenuer ness m	the study groups

Variable		Naproxen (n=26)	Diclofenac (n=26)	Piroxicam (n=26)	Placebo (n=26)	P-value
Clicking	First week	19 (73.1)	22 (84.6)	23 (88.5)	23 (88.5)	0.427
	Third week	13 (50.0)	17 (65.4)	19 (73.1)	20 (76.9)	0.175
	Fifth week	9 (34.6)	13 (50.0)	13 (50.0)	15 (57.7)	0.403
	Sixth week	9 (34.6)	12 (46.2)	12 (46.2)	15 (57.7)	0.426
	First week	12 (46.2)	16 (61.5)	16 (61.5)	21 (80.8)	0.083
Tondonnoog	Third week	9 (34.6)	13 (50.0)	13 (50.0)	19 (73.1)	0.049
	Fifth week	3 (11.5)	9 (34.6)	9 (34.6)	13 (50.0)	0.03
	Sixth week	2 (7.7)	9 (34.6)	8 (30.8)	13 (50.0)	0.011

Data are expressed as numbers (%).

#### DISCUSSION

Various treatment methods have been proposed for TMDs, which include patient education, conservative treatments, and various surgical procedures. Conservative treatments include physiotherapy, pharmaceutical therapy, and laser therapy, among others [8]. On the other hand, since 20%-30% of adults suffer from this problem, the treatment of TMDs is of great importance [17].

This clinical trial was performed to compare the effects of three NSAIDs (naproxen, diclofenac, and piroxicam) on TMDs. At baseline, all four groups were similar in terms of age, gender, VAS pain score, clicking, tenderness, and AROM. At 1 week, the study groups had no significant difference in the VAS pain score, clicking, tenderness and AROM. The study groups had no significant difference in the VAS pain score, clicking and AROM at 3, 5 and 6 weeks and only tenderness was significantly lower in the naproxen group compared to the placebo group.

Many researchers have assessed the effect of

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pharmacotherapy on TMDs, most of whom have emphasized on the effectiveness of pharmacotherapy for reduction of symptoms [17, 26, 29]. Moreover, no effective medication has been introduced in these studies [25, 30]. In a study on pain management in TMD patients, Alfonso Gil-Martínez et al. [31] recommended pharmacotherapy besides training of patients to more efficiently decrease pain. They also pointed to the optimal efficacy of naproxen, diclofenac, and piroxicam for pain reduction. In the present study, the patients were trained besides undergoing pharmacotherapy, and all three medications were effective for pain reduction by variable degrees.

Ouanounou et al. [32] evaluated the effect of pharmacotherapy on TMDs and found that naproxen reduced patients' symptoms more than celecoxib and placebo. Moreover, there was no significant difference between ibuprofen and piroxicam in patients with chronic pain. In the present study, naproxen had a greater analgesic effect than other drugs, and there was no significant difference between the placebo and piroxicam in pain reduction.

In a systematic review on the effect of invasive treatments on TMDs, Randhawa et al. [33] concluded that training patients could reduce their pain, especially in combination with other treatments. Similarly, in the present study, the placebo did not exert any effect on the placebo group, but since the patients were trained, improvement was seen in all four tested parameters.

Varoli et al. [19] examined the effect of splint therapy on 80 patients (35-70 years). They prescribed diclofenac, panacea (sodium diclofenac+ carisoprodol acetaminophen+ caffeine), and a placebo as adjuvant therapy with splint and found that splint in combination with diclofenac significantly decreased pain. The difference in the results between their study and the present study may be due to evaluation of different age groups and use of splint therapy in their study.

In another study by Ta and Dionne [17] on the TMJ pain, naproxen was more effective than celecoxib and placebo in pain reduction. In the present study, naproxen was also superior in

pain reduction. Roldan et al. [34] evaluated the analgesic efficacy of piroxicam, diazepam, and placebo in TMD patients and observed no significant difference among the three treatment groups. The results of the present study showed no significant difference between the piroxicam and placebo groups in pain reduction. Elder et al. [35] compared pain resolution in TMD patients by NSAIDs, the common medicines in China, and acupuncture. They reported greater reduction in VAS pain score in the NSAID group. The results of the present study showed that all the three drugs reduced the VAS pain score more than the placebo, and the mean pain intensity was significantly lower in the naproxen group than the placebo group in the first, third, fifth, and sixth weeks. Ekberg et al. [27] examined the effects of diclofenac and placebo on 64 patients with localized TMD pain over 2 weeks. They reported no statistically significant difference between the diclofenac and placebo groups. The current study also showed no significant difference between the diclofenac and placebo groups.

This study had some limitations. One limitation was that males and females were not investigated separately, and the effect of gender on treatment results was not evaluated. Moreover, the age range of patients was between 20 and 45 years. Evaluation of smaller age ranges can probably lead to more accurate results.

#### CONCLUSION

Naproxen tablets can reduce pain more than diclofenac tablets and piroxicam capsules. Regarding the tenderness, a significant improvement was observed in the naproxen group after 3 weeks of treatment. Moreover, naproxen, diclofenac, and piroxicam did not cause any change in AROMA and clicking compared to the placebo. Further studies are suggested to compare higher doses of these drugs.

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### CONFLICT OF INTEREST STATEMENT

None declared.

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