Diclofenac sodium as an alternative treatment of temporomandibular joint pain

EwaCarin Ekberg, Sigvard Kopp and Sigvard Åkerman

Department of Stomatognathic Physiology and Department of Oral Diagnosis, Centre for Oral Health Sciences, Lund University, Malmö, and Department of Clinical Oral Physiology, Center for Clinical Oral Science, School of Dentistry, Karolinska Institutet, Stockholm, Sweden

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In a double-blind study, diclofenac sodium (Voltaren®), 50 mg two or three times a day, was compared with placebo in 32 patients with pain localized to the temporomandibular joint (TMJ). The patients were allocated into two equally large groups. A visual analog scale was used to estimate the pretreatment degree of pain. The treatment effect was assessed as the frequency of joint and muscle pain and by the patients' own evaluation of improvement. The change in the clinical condition was assessed by tenderness to palpation of the TMJ and masticatory muscles and by mandibular mobility. The frequency of TMJ pain showed a greater reduction in the diclofenac group than in the placebo group, and there was a significant reduction of daily TMJ pain in the diclofenac group. The diclofenac group also showed a significant decrease in tenderness to palpation of the masticatory muscles in comparison with the placebo group. The patients with short duration of pain showed the best response to diclofenac. There was no evidence in this study to prove that diclofenac should be used as a primary treatment of TMJ pain, but it could be used as a complement to other treatments of acute TMJ pain. □ *Clinical trial; masticatory muscle; non-steroidal anti-inflammatory drugs; pain; placebo*

EwaCarin Ekberg, Department of Stomatognathic Physiology, Centre for Oral Health Sciences, Carl Gustafs v 34, S-214 21 Malmö, Sweden

Pain in the temporomandibular joint (TMJ) can be caused by different etiologic factors such as recurrent microtrauma (bruxism), trauma to the head and neck, degenerative joint disease, inflammatory joint disease, and disk derangement (1–3). This means that the patient population with pain in the TMJ is heterogeneous with regard to diagnosis and that the different subgroups of patients will be rather small in the clinic. In addition, the pain is often caused by several factors, and the etiology is therefore difficult to determine clearly.

The role played by inflammation as an underlying mechanism of pain and tenderness in the TMJ has been investigated (4), and radiographic, cellular, or biochemical signs of inflammation could be found in a high percentage of patients with pain in the TMJ. Wenneberg et al. (5) reported that intra-articular glucocorticosteroid injections often have a long-term palliative effect on the inflammatory signs and symptoms of the TMJ in patients with non-systemic inflammatory joint disease.

Non-steroid anti-inflammatory drugs (NSAIDs) have been used for a long time for several indications in this field. Numerous studies have investigated the short-term and long-term effect of diclofenac in other joints. These studies are mostly of patients with rheumatoid arthritis (6, 7) or osteoarthritis (8, 9), and they show a high anti-inflammatory effect of diclofenac. No controlled clinical trial has so far been performed in patients with pain in the TMJ to prove their value or to find out which patient groups benefit most from them (10). There might be a place for orally administered NSAIDs for TMJ pain, especially in the initial phase of treatment, when rapid pain relief is needed, and before other, perhaps more specific treatment such as splint therapy, optimal dental support (number of teeth and occlusal contacts), exercises for the jaw, intra-articular corticosteroid injections, or surgery can be applied.

The aim of this study was to compare the short-term effects of the NSAID diclofenac sodium (Voltaren®) with those of placebo in patients with TMJ pain.

Materials and methods

Patients

The clinical inclusion criteria for the study were age more than 20 years, presence of pain localized to the TMJ for at least 6 weeks, and lateral or posterior tenderness to the TMJ. The patients were not subjected to treatment of the TMJ with steroid or non-steroid anti-inflammatory drugs within the last 4 weeks before the trial. Criteria for exclusion were suspected or known general joint/muscle disease (for example, rheumatoid arthritis), symptoms that could be referred to disease in other components of the stomatognathic system (such as toothache, neuralgia), recent history of peptic ulceration

Table 1. Number of patients, distributed by sex, age, mean value of age, and duration of temporomandibular joint (TMJ) pain in the two patient groups

	Diclofenac, $n = 16$	Placebo, $n = 16$	Total, $n = 32$
Men	4	1	5
Women	12	15	27
Mean age (years)	48	46	47
Age range (years)	27–71	29–82	27–82
Duration of TMJ pain (months), median	8.5	12	11.5
Duration of TMJ pain (months), range	2–84	3–36	2–84
Duration of TMJ pain < 6 months	6	3	9
Duration of TMJ pain ≥ 6 months	10	13	23

or gastrointestinal bleeding, disorders of coagulation, pregnancy, nursing mothers, hypersensitivity to diclofenac or similar drugs, patients in whom acute asthmatic attacks, rhinitis, or urticaria could be precipitated by aspirin or other NSAIDs, patients with renal or hepatic diseases, and patients who did not want to take any oral medication. Of 2012 patients referred to the Dept. of Stomatognathic Physiology, Lund University, during 3.5 years, only 39 patients fulfilled the inclusion criteria and were consecutively included in the study. Seven of these patients withdrew from the study for different reasons. In spite of careful information, some of them did not want to take oral medication, and the others withdrew because of upper respiratory infections. Five of these belonged to the diclofenac group and the two others to the placebo group. Of the 32 remaining patients, 5 were men and 27 women, with ages ranging from 27 to 82 years (mean, 47 years) and with pain for an average of 17 months (Table 1).

Methods

Standardized protocols were used for the assessment of subjective symptoms as well as dental and medical history. The patients had to report duration of pain and TMJ pain at rest, on yawning, and on chewing. The level of pain was estimated by the patient at each visit as symptom-free, slight, moderate, severe, or unbearable. A 100-mm visual analog scale (VAS) (11) was given to the patients for daily reports of pain and dysfunction during the week before the actual trial was started. These values were used to compare the degree of pain between the experimental groups after randomization. The frequency of TMJ pain was asked about at each visit on the basis of an 8-unit scale: never, once a month, once a fortnight, once a week, twice a week, 3–4 times a week, daily, and constantly. At visits 2 and 3, the patients were also asked whether their symptoms were eliminated, much improved, improved, unchanged, impaired, or much worse compared with visit 1 (Table 2). Each patient was examined clinically before the medication was started (visit 1) and after 2 weeks (visit 2), when the medication was ended. After another 2

Table 2. Number of patients with signs and symptoms of temporomandibular joint (TMJ) pain before treatment (Visit 1), immediately after treatment (Visit 2), and after another 2 weeks (Visit 3) in the two patient groups

	Diclofenac, $n = 16$			Placebo, $n = 16$		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
TMJ pain evaluation						
Severe or very severe symptoms	10	6	7	9	7	8
Daily pain	15	11	10	16	12	15
Pain at rest	15			10		
Pain at rest (none or improved)		11	8		10	7
Pain on yawning	16			16		
Pain on yawning (none or improved)		10	7		7	7
Pain on chewing	15			14		
Pain on chewing (none or improved)		11	7		9	6
Signs						
Maximum opening capacity <40 mm	3	3	3	7	8	6
Deviation >2 mm during mouth opening	9	9	10	7	6	5
TMJ						
Soft-tissue swelling	3	1	0	0	1	2
Clicking	2	4	4	7	7	3
Crepitation	9	8	8	8	6	8
Lateral tenderness	16	10	9	16	10	13
Lateral and posterior tenderness	7	5	4	13	8	8
Masticatory muscles						
Tenderness of 1–3	9	7	5	6	4	7
Tenderness >3	6	4	6	8	10	8
Clinical dysfunction index I	0	4	5	1	2	3
Clinical dysfunction index II	6	6	5	1	3	4
Clinical dysfunction index III	10	6	6	14	11	9
Improved condition		6	8		4	5

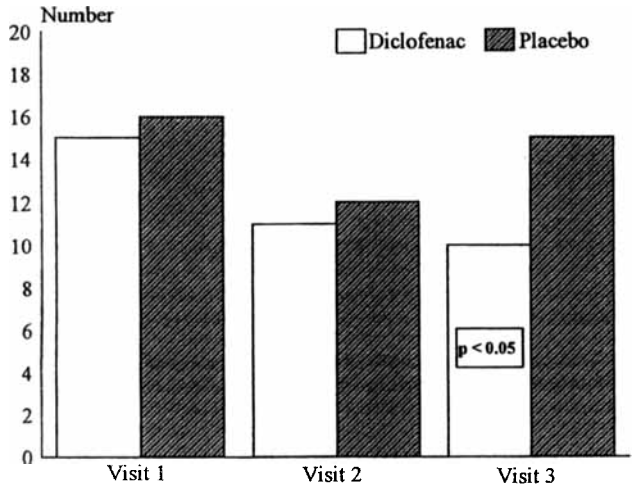

Fig. 1. Daily temporomandibular joint pain before treatment (Visit 1), immediately after treatment (Visit 2), and after another 2 weeks (Visit 3) in the two patient groups. There was a significant difference within the diclofenac group at visit 3 compared with visit 1 ($p < 0.05$).

weeks (visit 3) the treatment result was finally evaluated. All of the patients were examined by one and the same investigator at all visits, and both the investigator and patient were blind to the kind of treatment.

The clinical examination included assessment of pain during mandibular movements, palpation of the TMJ and masticatory muscles, registration of TMJ sounds (clicking and crepitation), assessment of soft-tissue swelling over the TMJ, measurement of mandibular movements, and deviation of the mandible during mouth opening. The severity of the clinical signs was estimated by the clinical dysfunction score and index in accordance with Helkimo (12).

After the first examination the patients were allocated at random to two equally sized groups of 16 individuals. One group was given 50-mg diclofenac enterotablets (Voltaren®, Ciba-Geigy Co.) three times a day during the 1st week, to rapidly reach an effective dose, and 50 mg twice a day during the 2nd week. The other group was given placebo of identical appearance and with the same dosage schedule. A rescue analgesic (paracetamol) was provided in case of intolerable pain during the trial. Fifty-nine per cent of the patients (19 patients) used this rescue drug, ranging from 1 to 20 tablets (mean, 7.8). Twelve of these patients belonged to the diclofenac group (mean, 8.0), and 7 belonged to the placebo group (mean, 7.0). Side effects of the drugs were recorded at visits 2 and 3. The treatment was considered to be of clinical value if both of the following criteria were fulfilled: 1) The patient reported the condition as improved or symptom-free; and 2) The value of the clinical dysfunction sum in accordance with Helkimo was reduced at least 5 units.

The study was approved by the Ethics Committee of Lund University.

Statistics

The statistical significance of the intra-individual treatment effect on subjective and clinical variables within groups was tested with the non-parametric Wilcoxon matched-pairs signed-ranks test. Differences in treatment results between the two groups were tested

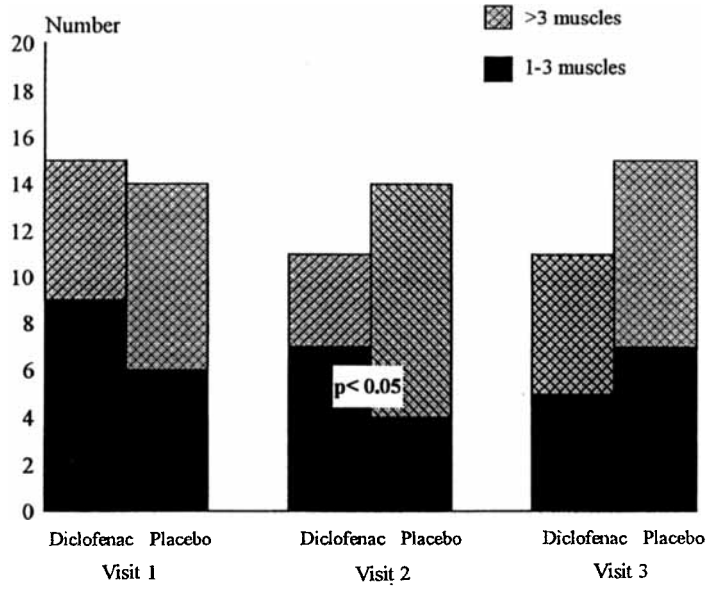

Fig. 2. Tenderness to palpation of the masticatory muscles before treatment (Visit 1), immediately after treatment (Visit 2), and after another 2 weeks (Visit 3) in the two patient groups. The difference between patient groups was significant after 2 weeks ($p < 0.05$).

with Wilcoxon's rank sum test. Frequency data were tested with the Mantel–Haenszel method.

The 5% level was chosen as the level of statistical significance.

Results

Before treatment

The patient groups were comparable to each other before treatment with regard to all variables except location of the TMJ tenderness, clickings, maximum opening capacity, and variation in age (Table 2). The mean value of the VAS before treatment was 60 mm for all patients, 66 mm for the diclofenac group, and 54 mm for the placebo group. The difference between the two groups was not statistically significant. Seventy-two per cent of the patients had experienced pain in the TMJ for more than 6 months (Table 1). Daily or constant pain was reported by 98% (Fig. 1). Pain in the TMJ at rest was reported by 78% of the patients. Almost every patient reported pain in the TMJ during yawning and chewing (Table 2). All of the patients were tender laterally to the TMJ, and two-thirds of the patients were tender both laterally and posteriorly. Tenderness to palpation of the masticatory muscles was found in 90% (Fig. 2). Eighty-one per cent of the patients had sounds from the TMJ. Soft-tissue swelling over the TMJ was found in only three patients. The mean of the maximum opening capacity was just above 40 mm in both groups. According to the clinical dysfunction sum, 75% of the patients had severe dysfunction (Table 2).

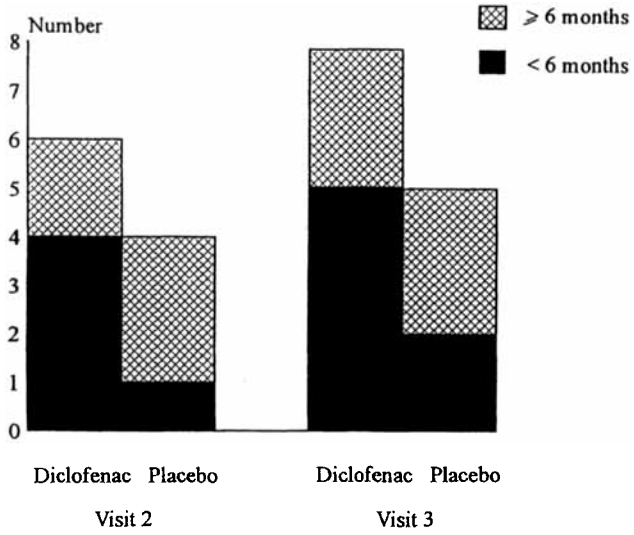

Fig. 3. Responders to treatment in relation to duration of temporomandibular joint pain in the two patient groups.

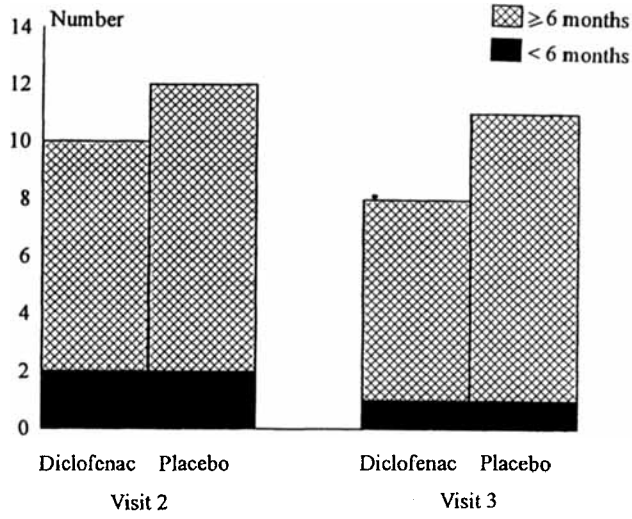

Fig. 4. Non-responders to treatment in relation to duration of temporomandibular joint pain in the two patient groups.

After treatment

There was a significant reduction in the frequency of TMJ pain in the diclofenac group at visit 3 ($p < 0.05$) compared with visit 1 (Fig. 1), but there was no significant difference between the groups. Nor was there any significant difference between the groups with regard to level of pain. Seventy-eight per cent of the patients reported moderate or severe pain in the TMJ at visits 2 and 3. At visit 3, 38% of the patients in the diclofenac group and 25% of the patients in the placebo group reported an improved condition, but this was not statistically significant. Pain in the TMJ at rest, during yawning, and on chewing decreased in both groups, but no statistically significant differences were found within or between the groups (Table 2). Just after the termination of medication (at visit 2), 38% of the patients in the diclofenac group had no tenderness of the TMJ, and 44% of the patients in this group were free from tenderness after another 2 weeks. The corresponding values for the placebo group were 38% and 19%, respectively. Tenderness to palpation of the masticatory muscles showed a significantly greater reduction at visit 2 in the diclofenac group than in the placebo group ($p < 0.05$) (Fig. 2), but this reduction was not present at visit 3. Among the six patients in the diclofenac group with a pain duration of less than 6 months, five had a reduction of muscle tenderness at visit 2 and four at visit 3. The corresponding figures for a duration of more than 6 months were five at visit 2 and two at visit 3, respectively. There were no statistically significant differences within or between the groups with regard to TMJ sounds, soft-tissue swelling over the TMJ, mouth-opening capacity, or deviation of the mandible during mouth opening (Table 2). The clinical dysfunction sum did not decrease significantly in any of the groups, but the reduction

observed was greatest in the diclofenac group. The evaluation of the clinical value of the treatment on the basis of the present criteria showed no significant differences between the treatments. When the diclofenac group was divided on the basis of these criteria into responders (6 patients) and non-responders (10 patients), we found that 67% of the responders (Fig. 3), compared with 20% of the non-responders (Fig. 4), had had TMJ pain for less than 6 months. Five patients reported side effects such as gastric pain, vomiting, diarrhea, tiredness, or xerostomia, and all of them belonged to the diclofenac group.

Discussion

When evaluating our results, it should be borne in mind that the study comprised small groups. In spite of a large number of referred patients during 3.5 years, there were only 39 patients who fulfilled the rigorous criteria. Most of the patients showed high severity of signs and symptoms. There should therefore still be a good chance of detecting clinically significant treatment effects. The groups were comparable with regard to all variables before treatment except location of tenderness to palpation of the TMJ, clickings, maximum opening capacity (<40 mm), and variation of age, and consequently, the comparison between diclofenac and placebo should be valid for all other variables.

Since we have not recorded any radiologic, cellular, or biochemical signs of inflammation in this study, we prefer to use the term TMJ pain instead of TMJ arthritis.

The study was double-blind, and all patients received the same information and tablets of identical appearance. It could be expected from the results of previous studies that 33–66% of the placebo group would respond (13), but the response rate in this study was 31%. Placebo seems to be most effective when the painful or stressful condition is severe, and its potency seems to be greater when the pain is acute rather than chronic (13). In our study most patients (72%) in both groups had chronic pain—that is, of longer duration than 6 months (Table 1). Our results are therefore in agreement with those of Epstein (14), who considered that the placebo effect is significant also for symptoms of chronic conditions including pain, depression, and anxiety.

The finding that the maximum mouth-opening capacity did not increase in the diclofenac group even though the tenderness of the masticatory muscles decreased might be explained by decreased translatory mobility within the TMJs. It has also been reported that chronic muscle pain may be associated with muscle atrophy and fibrosis (15).

Only 44% of the patients in the diclofenac group were completely free from joint pain at visit 3, which suggests that part of the joint pain and tenderness was of non-inflammatory origin—that is, not mediated by prostaglandins. The enzyme cyclooxygenase, which participates in the synthesis of prostaglandins, is the main target for NSAIDs. However, leukotriene B_4 (LTB_4) and prostaglandin E_2 (PGE_2) have been found in the synovial fluid of patients with chronic TMJ pain and dysfunction (16). Both these lipids are strong mediators of pain and inflammation. NSAID inhibits only PGE_2 synthesis (cyclooxygenase), whereas glucocorticoid also inhibits LTB_4 synthesis (phospholipase A_2). This condition can explain the insignificant decrease in the level of TMJ pain accomplished with NSAID in this study compared with the effect of treatment with intra-articular glucocorticoid (5). It was a remarkable finding that muscle tenderness was reduced more in the diclofenac group than in the placebo group, suggesting that part of the muscle tenderness is of inflammatory origin, at least in the early phase (<6 months).

When the groups were divided into subgroups with acute (<6 months) or chronic (≥6 months) pain, no statistically significant difference with regard to pain or assessment of treatment success could be found, but the patients with short duration of pain showed the best response to diclofenac in this study. Chronic TMJ pain is probably more efficiently treated with other means (17, 18), since it seems to a large part involve pain mediators not responding to NSAID.

There was no evidence in this study to prove that diclofenac should be used as a primary treatment of TMJ pain, but it could be used as a complement to other treatments of acute TMJ pain.

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