

Impact of Medication with Diclofenac Sodium vs. Etoricoxibum in Patients with Inflammatory Rheumatic Pathology, Prosthetic Complications and Algo-dysfunctional Syndrome

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Affections of temporomandibular joint (TMJ) can lead to imbalances and disfunctions named algodysfunctional syndrome. One of the affections that we will take into consideration in this study is the temporal-mandibular arthrosis, which is, in fact, the frequent pathology at this level, and to which we will measure the pain before and after the administration of the anti-inflammatory therapy: Etoricoxib vs. Dyclofenac. The important objective of this study is to investigate this type of drug treatment over TMJ. The class of drug called non-steroidal anti-inflammatory drugs (NSAIDs)—so called to distinguish this class of drug from steroids, which have similar but additional effects—make NSAIDs one of frequently used drugs for the symptomatic treatment of many common conditions. Etoricoxib is clinically effective in the therapy of TMJ providing a magnitude of effect comparable to that of the maximum recommended daily dose of Diclofenac.

Keywords: anti-inflammatory medication, rheumatoid arthritis, algodysfunctional syndrome, prosthetic treatment, the temporal-mandibular joint (TMJ).

Rheumatic diseases are the second leading cause of global disability, according to World Health Organization (WHO) data [1]. Rheumatoid arthritis affects small joints, causing pain, inflammation, stiffness and, over time, loss of mobility. The *Rheumatoid Arthritis Classification Criteria* were introduced in 2010 [2]. According to the recent studies, the disease accounted for about 10% of all rheumatic diseases. In the context in which adult people are affected and the disease has a severe, chronic and invalid progression, it is not only a medical problem but also a social one [3].

Approximately 143,000 of the Romanian population are affected by rheumatoid arthritis (1% disease prevalence and 40 new cases per 100,000 inhabitants, the incidence is higher for women compared to men, the gender ratio being F/M = 2-3/1). The average age at onset is between 25-40 years [4]. In the context of rheumatoid arthritis as the underlying disease, the temporomandibular joint (TMJ) is affected in 18% of patients [5].

The dysfunctional syndrome of the stomatognathic system (DSSS) presents not only a complex etiopathogenesis, but also a complicated symptomatology, in which the signs of the dysfunctional affection of the stomatognathic system are countless, as well as the associated signs which incorrectly conduct the diagnosis to the nearby area [6, 7].

Temporomandibular joint, one of the frequent affected elements of the stomatognathic system from the dysfunctional syndrome, is mainly based on the modification of the patterns of the articular moves and on the inflammation of

the micro-traumatism (rheumatic disease) that appear in cases of dysfunctions with a starting point in the TMJ [6, 8].

The analgesic (pain relieving), anti-pyretic (fever reducing), and anti-inflammatory (inflammation reducing) properties of the class of drug called non-steroidal anti-inflammatory drugs (NSAIDs) — so called to distinguish this class of drug from steroids, which have similar but additional effects — make NSAIDs one of the most frequently used drugs for the symptomatic treatment of many common conditions [9]. Their effect is to reduce or eliminate some symptoms and signs of the inflammation in rheumatic diseases. For patients with musculoskeletal disorders, conventional NSAIDs form the mainstay of clinical care.

Anti-inflammatory drugs are divided into two major classes: classical nonsteroidal anti-inflammatory drugs (first generation) and selective or specific cyclooxygenase enzyme 2 (COX-2) inhibiting nonsteroidal anti-inflammatory drugs (second generation). NSAIDs are a group of drugs that inhibit both the isoforms of cyclooxygenase enzyme [10]. Conventional NSAIDs are nonselective, which bind and inhibit both the isoforms, but cyclooxygenase-1 (COX-1) is inhibited more avidly than cyclooxygenase-2 (COX-2) [11]. Inhibition of COX-1 is responsible for the side effects and that of COX-2 for therapeutic effects. This has resulted in the introduction of the COX-2 selective drugs [12]; COX-2 inhibitors are newer generation drugs, with more reduced side effects, but not free of them, and with lower potency than NSAIDs [13].

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Experimental part

Aim and objective of the study

Affections of TMJ can lead to imbalances and dysfunctions named DSSS. The TMJ affections we will take into consideration in this study, which is, in fact, the frequent pathology at this level, and to which we will measure the pain before and after the administration of the anti-inflammatory therapy.

The aim of this study is to investigate the drug treatment of TMJ and the main objective is to realize a comparison between I-st generation derivate, Diclofenac sodium and a derivative of II-nd generation, Etoricoxibum.

Material and method

This is a prospective study, based on data obtained from 531 patients with rheumatoid arthritis pathology, 96 (18.07%) of them with TMJ affected and DSSS, hospitalized at the Clinic of Rheumatology, Clinical Rehabilitation Hospital Iasi, between 01.01.2015 and 31.12.2016. The endpoints of interest were pain, physical function and patient global assessment of disease status (PGADS).

Patients were informed about the study and the content of the questionnaire. When patients were willing to participate, they were requested to fill an informed consent. The study was approved by Committee of Research Ethics from Grigore T. Popa University of Medicine and Pharmacy, Iasi.

Data concerning physical health were retrieved from patients with painful temporal-mandibular disorders according to the research diagnostic criteria.

The inclusion criteria for the patients in our study were: all patients had to have experienced pain complaints in the temporal-mandibular region for at least 1 month, the presence of muscular tonus and muscular contraction alterations muscular dysfunction (pain at the level of stomatognathic system and cephalic extremity, limitation of mouth opening, and deviation of mandible from the medial line during the opening, fatigue of cephalic extremity muscles and functional alteration of stomatognathic system). Participants admitted or keeping follow-up appointments were also included.

The exclusion criteria of the patients were represented by the presence of joint affliction, of the third molar pathology, osteoarthritis and neoplasm [14, 15]. Exclusion criteria were also: refuse of the patient to participate, uncooperative patients or those who did not respect the prescribed treatment. In addition, patients with confirmed congestive heart failure, ischemic heart disease, peripheral arterial disease and cerebrovascular disease were excluded from the group treated with Diclofenac sodium. Also, from the group treated with Etoricoxib, were excluded the patients with gastric ulcer, gastrointestinal haemorrhage, inflammatory bowel disease, bronchial asthma, salicylates allergy or to other non-steroidal anti-inflammatory drugs, hepatic failure, renal failure, myocardial infarction, stroke, and hypertension at which the blood pressure levels are not adequately controlled, age 65 years [16].

Patients were introduced in the Mihail Kogalniceanu Clinical Education Base, of Iasi for prosthetic and gnathologic treatment, the methodology of clinical and paraclinical examination being applied, including the TMJ and occlusion examination, as well as TMJ tomography. An objective examination of the TMJ has been realized.

For this study there were taken into consideration the symptoms of the patients, which determined their addressing to the doctor. The most common symptom is the pain, which appears in front of the ear or near to it, with propagation towards the cheeks, neck, shoulder, which is present in all our patients considered in this study.

In our study, we administered two anti-inflammatories frequently used in the TMJ treatment: Diclofenac [Sodium-(0-(2,6- dichlorophenyl) -amino-phenyl) acetic acid, a phenylacetic acid derivative (fig. 1)], 150 mg/day and a derivative of II generation, (Etoricoxibum), 5-chloro-6'-methyl-3-[4-(methylsulfonyl) phenyl]-2,3'-bipyridine in doses of 30 or 60 mg/day for a period of two weeks (fig. 2).

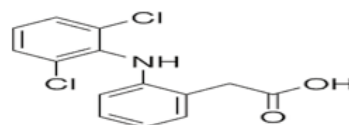


Fig. 1. Chmical formula Sodium diclofenac

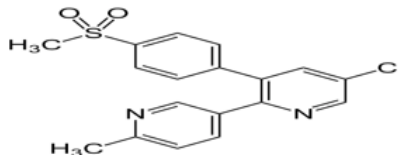


Fig. 2. Chemical fomula for Etoricoxibum

Diclofenac sodium and Etoricoxib have been used to relieve pain and inflammation of the joints and muscles. For all patients, we used the lowest effective dose and shortest treatment duration to control the symptoms.

A database was generated using Microsoft Excel 2010 for Windows and the SPSS statistical software package (version 18.2 for Windows; SPSS, Inc., Chicago, IL, USA) was used in order to perform the statistical processing of data and statistical analysis [17].

Statistical analysis

The obtained data were allowed for the classification of patients with respect to gender distribution, age groups, area or origin, clinical aspects, type of treatment instituted and appreciation of pain.

Results and discussions

General characteristics

Thereby, we classified the patients included in this study on age groups: 20-29 years- 9 (9.37%) patients, 30-39 years- 15 (15.63%) patients, 40-49 years- 60 (62.50%) patients and 50-59 years-12 (12.50%) patients. A significant statistical difference between the medium age groups, 40-49 years and the other groups ($p < 0.001$) may be noticed.

Another variable taken into consideration is the gender distribution. Our study included 66 (68.75%) female patients and 30 (31.25%) male patients. Between the two gender groups studied there was a statistically significant difference ($p < 0.001$). The results are consistent with the data found in the literature [4], the gender ratio being $F/M = 66/30 = 2.2/1$ (fig. 3).

The patients are divided depending on the social environment. Thus, in our study there were 56 (58.33%) patients from the rural area and 40 (41.67%) patients from the urban area (fig. 4).

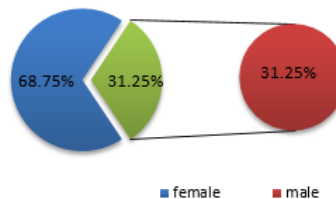


Fig. 3. Gender distribution

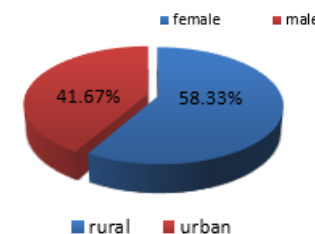


Fig.4. Distribution based on social environment

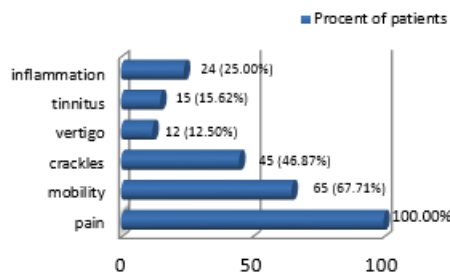


Fig. 5.
Symptomatology
of the patients
with DSSS

Symptomatology that indicate the DSSS in patients (that were presented in our services, in the Mihail Kogalniceanu Clinical Education Base), like pain, mobility, crackles, vertigo, tinnitus, inflammation, were revealed in figure 5.

The articular affectionation

Pain and articular noises affect in a high percentage the studied group, which is due both to edentation grade (complications of it) and the chaotic, uncoordinated, functioning of the stomatognathic muscle system, especially of the external pterigoid (table 1).

Table 1
THE ARTICULAR AFFECTATION

Clinical sign:	Affected patients	
	Number	(%)
Articular pain	10	30.30
Articular salt	16	16.49
Deviation of the mandible	20	20.61
Subluxation	-	-
Limitation of the mouth opening	18	18.55
Crackles	28	28.86
Articular blockage	-	-

The muscular affectionation

The examination of the muscles is made by inspection and palpation in order to determine the painful points and the irradiation areas. Any painful areas, trigger areas with determinations at distance, as they are noted in the observation paper, circumscribing the painful area at direct palpation, trigger area, irradiation area. The examination of the muscles in dynamic aims to detect the pain provoked by contraction, symmetric and equal participation in the realization of the mandibular dynamic (table 2).

Table 2
THE MUSCULAR AFFECTATION

Clinical sign:	Affected patients	
	No.	(%)
Muscular pain	10	30.30
Muscular hypertonia	33	100.00
Muscular spasm	33	100.00
Muscular hypertrophy	20	60.60
Muscular fatigue	33	100.00
Limitation of the mandibular movement	28	84.85
Dynamic modification of the mandible trajectory	26	78.79

Signs and muscular symptoms are predominant in the clinical table, being almost impossible to clearly establish the cause of the signs and symptoms, such as rheumatoid arthritis pathology or as a consequence of edentulous. The clear influence could be studied after prosthetic patients, when the influence would remain only in patients with rheumatoid arthritis pathology.

Affectionation of the muscular factor, important milestone in the correctitude of the cranial-mandibular fundamental relations will implicitly generate the installation of cranial-mandibular relations.

Modification of the cranial-mandibular relations

Examination of the centric relation has a major impact in establishing the diagnosis of the stomatognathic system's dysfunctions (table 3).

Interarcadic reports registered in centric relation will serve to detect the premature contacts (where applicable) in centric relation or at fitting models in the articulator.

Table 3
THE CRANIAL-MANDIBULAR RELATIONS

Name of the malrelation:	Affected patients	
	No.	(%)
Extrapostural malrelation (I)	16	16.49
Excentric malrelation (II)	7	7.21
Extrapostural-excentric malrelation (III)	10	10.30

Modification of the main functions: masticatory, deglutition, physiognomic, phonetic and latching occurs in the whole group of patients, so the prevalence is 100%, each patient being total or subtotal edentulous, showing damage physiognomy, a self-maintaining circuit, speaking problems, masticatory issues or dysphagia for liquids and solids.

In case of dynamic occlusion the testing movement is realized, testing position with contact at the level of all the incisors (normal) and a distal occlusion (Cristhensen sagittal). It is observed the way in which dynamic occlusion is in compliance with mandibular dynamic, articular dynamic or muscular contraction (table 4).

Table 4
MODIFICATIONS OF THE OCCLUSION

Modifications of the occlusion:	Affected patients	
	No.	(%)
Modifications of the dynamic occlusion	33	56.70
Modifications of the static occlusion	10	10.30

Articular pain is of variable intensity, starting with dull vivid pains, up to real uni- or bilateral pain, it appears at rest and can be exacerbated in motion, usually in the morning, disappearing after a few moves. It can also appear after lunch, as a result of the fatigue and joint solicitation. It is a disorder of the TMJ, which frequently determines patients to ask for treatment, because they usually do not realize the existence of the crackles or other functional disorders.

Another variable taken into consideration is the articular mobility, and the third obvious sign are the crackles produced when using the articulation, which can be heard by the patient and also by the ones around him, but which are not significant in the absence of the pain and articular immobility. From the mobility point of view, in our study articular hypermobility can be found in 41 (42.71%) patients, which is much more frequent than the limitation of the mandible movements, which is present in 24 (25.00%) patients (fig. 6). Between the two parameters there is a statistically significant difference ($p < 0.001$).

Making proper medical history of the patient revealed a history of bruxism, trauma, local infection, stress and rheumatoid arthritis (fig. 7).

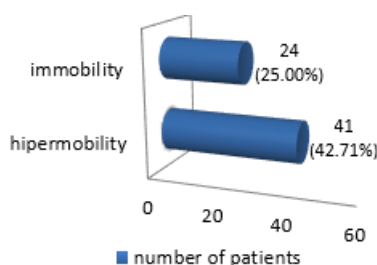


Fig. 6. Mobility in the TMJ

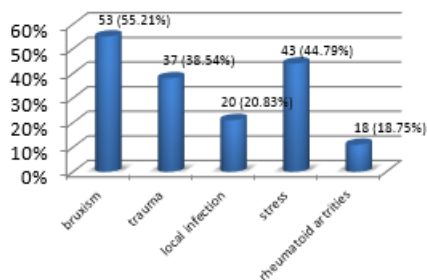


Fig. 7. Personal pathological antecedents

For the treatment of the pain it was used Diclofenac at a dose of 150 mg and Etoricoxib, in doses of 30 and 60 mg. Each group included 32 patients each. They were questioned and evaluated immediately after the treatment (4 h), after two days and after two weeks of treatment about the pain threshold according to VAS (Visual Analogue Scale).

Etoricoxib (60 mg) demonstrated a significantly greater benefit within 4 h of the first dose (fig. 8) on the first day of therapy ($p = 0.001$) as evaluated by the percentage of patients with good or excellent responses (values 1-3 VAS).

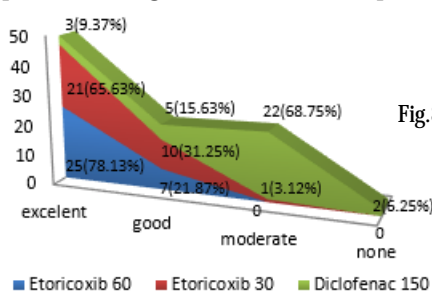


Fig. 8. Effect of the NSAIDs after 4 h

The effect of Diclofenac is moderate at this time and seemed significantly lower than after the administration of Etoricoxib (fig. 9). Moreover, the use of the two doses of Etoricoxib highlights a stronger effect on a higher dose, but is not statistically significant.

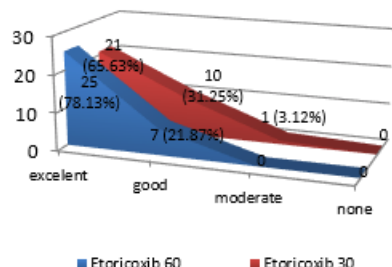


Fig. 9. Comparison of the effect of Etoricoxib

The second interrogation of the patients took place after two days. It seems that the effects have been similar, no matter what anti-inflammatory was used, the patients declaring that they felt a moderate pain, significantly lower than the one they felt in the initial moment of the administration. Even though, it can be noticed that the patients who were administered Etoricoxib 60 mg were predominant in the group with the lack of pain and minimum pain. The last evaluation was conducted after two weeks of treatment.

Etoricoxib 30 mg determined a moderate reduction (maximum number of patients) of the pain threshold. So, the Etoricoxib demonstrated at least moderate clinical improvements.

Diclofenac 150 mg resulted in at least small improvements (fig. 10).

The effects of the anti-inflammatories were preserved throughout the administration, without any significant changes (fig. 11). It can also be mentioned that improved outcome was not only in terms of pain but also in terms of clinical function of the TMJ.

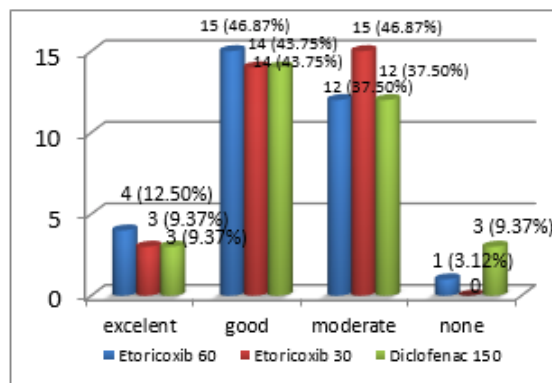


Fig. 10. Effects of the NSAIDs after 2 days

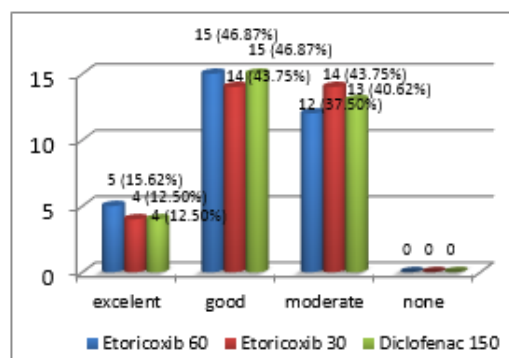


Fig. 11. Effects of the NSAIDs after 14 days

Another important parameter that we took into consideration was the side effects of the anti-inflammatories. They cause side effects including gastrointestinal (GI) disorders (from minor dyspepsia through to ulcers, bleeding and perforation), kidney effects and cardiovascular effects. It has been proposed that COX-2 inhibitors result in anti-inflammatory and analgesic properties, similar to what can be achieved with conventional NSAIDs. However, by sparing COX-1 activity, selective COX-2 inhibitors have greatly reduced toxicity, particularly in GIT [10]. In our study there were no usual side effects during the administration of any of the used drugs, with the condition of respecting the basic rules. In considering the risk associated with non-prescription use of NSAIDs, it is important to consider three factors: safety at low doses, with short durations of treatment, and in populations with a low background risk of events [13, 17].

The economic evaluation demonstrated that Etoricoxib (60 mg) is an economically superior treatment to that of Diclofenac (150 mg) for both QALY gains and cost savings for a time horizon longer than 5 years [18]. For a 1-year time horizon, Etoricoxib is associated with greater costs than Diclofenac (150 mg), but can still be considered cost effective [19, 20].

Patients have been applied, simultaneously, different fix prosthetic treatments, mobile, as well as relaxation mouth guards (fig. 12), an improvement of the quality of life of these patients being registered, as it follows: in 75% were applied acrylic prostheses and in the rest, both fixed and

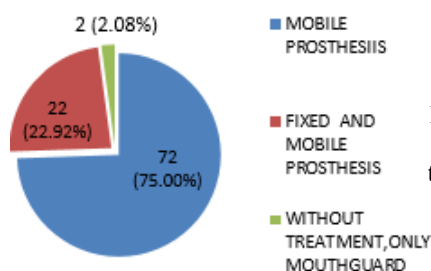


Fig. 12. The prosthetic and gnathologic treatment of the study patients

mobile, only in 2 (2.08%) cases being used the method of relaxation mouth guards.

Conclusions

Both treatments were generally well tolerated. Etoricoxib is clinically effective in the therapy of TMJ providing a magnitude of effect comparable to that of the maximum recommended daily dose of Diclofenac.

The onset of clinical benefit with Etoricoxib on day one is more rapid than that of Diclofenac, both were generally well tolerated.

It should also be mentioned that the improved outcome of the patients was not only in terms of pain but also clinically, meaning at the TMJ function.

Contribution of the authors:

Associate Professor, Carausu Elena Mihaela MD, PhD-study design, literature search, and manuscript preparation;

University professor Rezus Elena, MD, PhD- collection of the data from the study group, clinical diagnosis and clinical interpretation of the results rheumatology treatment;

University assistant Checherita Laura Elisabeta, MD, PhD-collection of the data from the control group and the prosthetic treatment;

Lecturer Maria Magdalena Leon, MD, PhD- collection of the data from the study group, clinical diagnosis and clinical interpretation of the results, statistical processing of the data.

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