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Effectiveness of Analgesics in the Treatment of Temporomandibular Dysfunction: A Systematic Literature Review

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ABSTRACT

Introduction: *Temporo-mandibular dysfunctions correspond to a defect adaptation of the manducatory apparatus. Different therapeutic methods are available for the treatment of these pathologies: Splints, physical therapies, occlusal therapies, surgery or pharmacological treatments. The objective of our work is to analyze the clinical effectiveness of analgesics in the treatment of disorders of the masticatory apparatus by applying the Evidence approach Based Dentistry.*

Methods: *The collection of data from the literature scientific was carried out among the production that appeared during the period from 2011 to 2021. The documentary research was carried out using accessible databases via the Internet namely MEDLINE, ELSEVIER and Cochrane Database of Systematic through their PubMed, Science Direct and Cochrane library search engines, as well as the website Google Scholar. A bottom-up manual search covering the same study period was carried out in order to enrich our bibliography. The writing of this systematic review followed the guidelines of the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).*

Results: *9 relevant randomized clinical trials were selected after critical reading guided by the CASP type reading grids. The items have been listed in 4 categories according to the route of administration of the analgesics (topical route, oral, intramuscular route and intra-articular route) and classified in tables according to the PICO criteria (Participants/Interventions/Comparison/Results "Outcomes"). The results of our study show a significant reduction in the intensity of the pain and the rates of cytokines as well as a significant increase in maximum mouth opening.*

Conclusion: *The use of analgesics increases the efficacy of treatment by decreasing pain intensity and cytokine levels, through both their analgesic and anti-inflammatory actions. This efficacy is similar for both levels II and III. However, additional long-term clinical studies with a larger sample size are needed to confirm the data collected and to further explore the effect of analgesics in the treatment of TMDs.*

Keywords

Neuromuscular system, Temporomandibular joint Disorders, Pharmacological therapies.

Introduction

The manducatory apparatus is a system formed by several components; a passive articular component (temporomandibular and occlusal) and an active muscular component, which maintain reciprocal relations of influence between them, in coordination with the neuromuscular system [1]. The health of this apparatus is maintained by a coordinated, interdependent, and harmonious functioning of its determinants. A lack of adaptation

of this apparatus can be responsible for several pathologies (osteoarthritis, disc dislocation, myofacial pain, musculo-articular pathologies...). The absence of a systematic taxonomy for all these disorders means that they are grouped under global terms such as "craniomandibular dysfunctions or disorders (CMD)", or "temporomandibular disorders".

Temporomandibular joint Disorders (TMD). This term is defined as the symptomatic expression of a pathology that can be originating from muscles, joints, or a combined one. This includes anatomical, histological, and functional abnormalities of the muscular and articular systems [2]. The three characteristic signs of these disorders are noise (clicking, clenching, clacking), pain (aching), and dyskinesias [3]. The multitude of symptoms of these disorders results from the great number and the intricacy of the biological, structural, and psychosocial cofactors implied in the triggering and evolution of these dysfunctions [4].

This multifactorial character makes therapy and prognosis more complicated and leads the patient to under diagnosis or therapeutic wandering. Global treatment aims at reducing pain, improving function, and acting on psychism. For this purpose, different therapeutic approaches are available, such as maxillofacial physiotherapy [5], therapeutic education, cognitive-behavioral therapies, hypnosis [6], relaxation, the use of occlusal orthoses [7], and pharmacological therapies (analgesics, anxiolytics, anti-inflammatories, muscle relaxants, antidepressants, etc.) Many clinical studies on peripheral opioid analgesia have been developed in patients with persistent joint pain, a problem of major relevance and prevalence. Of these, temporomandibular joint (TMJ) pain has long been recognized as one of the most difficult types of joint pain to treat [8].

The most commonly considered analgesics for oral administration are codeine and oxycodone, with hydromorphone reserved for severe intractable pain. If oral administration is not a reasonable option, patches may be considered for those trained in its use [9]. Parenteral injection of analgesics (intramuscular, intradermal, intra-articular, etc.) is most commonly used for the treatment of TMD, especially in combination with arthrocentesis [10]. Analgesics act by binding to specific cell receptors in the central and peripheral nervous systems [11], which play a key role in modulating pain and inflammation [12]. There is recent evidence for the existence of a peripheral subtype of the μ-opioid receptor in TMJ tissues [13], thus explaining the possible benefits of this treatment modality. However, many theories consider the use of analgesics to be only a symptomatic and palliative treatment; without treating the cause, relieving pain will eventually reappear. This lack of consensus concerning the place of analgesics in the management of disorders of the manducatory apparatus causes practitioners to be confused about the use of these molecules. In light of the above, this thesis proposes to conduct a systematic review by applying the Evidence-Based Dentistry approach, with the main objective of evaluating the clinical effectiveness of analgesics in the management of manducatory dysfunction.

Materials and Methods

Research Strategy

The literature search was based on scientific databases accessible via the Internet. An electronic search was carried out using the international databases MEDLINE, and ELSEVIER through their search engines; respectively PubMed, Science Direct, as well as the Google Scholar site. The collection of data from the scientific literature was carried out among the scientific production that appeared during the period from January 2011 to January 2021. The electronic search strategy was carried out using the following keywords: Temporomandibular joint disorders, Craniomandibular disorders, Analgesics, Analgesics, opioids, Analgesics, and Non-Narcotic. These terms were then combined through Boolean operators to arrive at the Boolean equations below: "Temporomandibular joint disorders" (Mesh) And" Analgesics ″(Mesh), "Craniomandibular disorders" (Mesh), And "Analgesics" (Mesh), "Temporomandibular joint disorders" (Mesh) And "Analgesics, Opioid" (Mesh), "Temporomandibular joint disorders" (Mesh) And "Analgesics, Non-Narcotic" (Mesh).

Eligibility Criteria

Inclusion Criteria: Articles included in our literature search were randomized controlled trials that met all of the following inclusion criteria: studies with a publication date between 2011 and 2021, written in French or English, human studies, low dropout rate, identical follow-up between groups, adequate statistical analysis.

Exclusion Criteria

Articles were excluded if they met any of the following criteria: studies with publication dates before 2011, animal studies, anti-inflammatory studies, case series, retrospective studies, literature reviews, letters to the editor, and studies funded by manufacturers.

Literature Selection Strategy

Two readers to reduce the risk of excluding relevant studies, minimize the risk of judgment error and subjectivity, and ensure the reproducibility of results performed study selection and quality assessment independently. This approach was also used for data extraction, which is particularly prone to error. In case of discrepancies, the articles concerned were discussed between the two readers to reach a consensus. The initial electronic search was carried out on various search engines. The selection was made initially by two readers (B.I., G.M.) based on titles and abstracts. The same readers according to the eligibility criteria analyzed the selected articles. The Critical Appraisal Skills Programme (CASP) critical reading grids (Appendix 1) guided the full-text reading. This second step allowed the final selection of potentially eligible articles. After having explored all the electronic databases mentioned above using search engines, the bibliography of the selected articles was finally studied to detect other articles following the same path as our study.

Risk of Bias (Methodological Quality Assessment)

The critical reading of the articles was based on 2 tools for assessing methodological quality. The first tool is the CASP

checklist (Critical Appraisal Skills Programme): this tool proposes 11 questions. The first two questions are filter questions, to which the answer is quick. If the answer is positive, it is appropriate to move on to the next questions. The second one is the risk of bias assessment from the "Cochrane Handbook for Systematic Reviews of Interventions" adapted and updated by Higgins and colleagues in 2011. It includes Selection bias: Which refers to systematic differences in the baseline characteristics of the groups being compared. To limit the risk of selection bias, the method for generating the randomization sequence must be appropriate and the principle of secret assignment must be respected. Performance bias: Refers to systematic differences between groups in the care of participants. To limit the risk of performance bias, participants and the health care team should be blinded to the interventions received. Detection bias: Refers to systematic differences between groups in the way the outcome is assessed. To limit the risk of detection bias, the evaluator should be blinded. Attrition bias: Refers to systematic differences between groups regarding withdrawals of participants from the trial. Publication and selective reporting bias: Refers to systematic differences between reported and unreported outcomes. Other biases: In addition, other sources of bias are relevant in some circumstances. For each article, the risk of bias estimate was divided into 3 categories "High risk," "Minimal risk," and "Uncertain risk." The judgment criteria for estimating the risk for each bias were listed in the risk of bias assessment tables.

Writing Protocol

The writing of this thesis work followed the guidelines of the PRISMA Statement "Preferred Reporting Items for Systematic reviews and Meta-Analyses" considered as a writing guide according to Moher et al. in 2009, helping authors to write their systematic literature reviews or meta-analyses by evaluating all clinical trials in response to a specific clinical question.

Results

The results of our search are presented in the form of a flow chart (Figure 1) exposing the choice of the selected articles. A general description of the studies will be highlighted in a table, and then the articles will be categorized according to the route of administration, and classified in tables according to the PICO criteria (Participants/Interventions/Comparison/Outcomes).

Selection of Articles

Flow Chart

The selection of the articles followed several steps presented in the form of a flow chart suggested by "The PRISMA Statement.

Figure 1: Flow chart illustrating the different stages of publication selection in the systematic literature review.

Descriptive Results

Description of results according to PICO criteria:

The studies were classified into four main categories: Administration of topical analgesics, Administration of oral analgesics, Administration of intramuscular analgesics, and Administration of intra-articular analgesics. This category was subdivided into two other categories according to the variables studied: Analysis of cytokine changes and Analysis of pain intensity, maximal mouth opening, clicking sounds, and/or mandibular movements. The description of the articles included in our review was carried out according to the PICO criteria (Participants/ Intervention/ Comparison/ Outcomes).

Risk of Bias in Included Studies

Bias was assessed using the tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions "The Handbook" online guide adapted by Higgins et al. in 2011.45 this tool is used to estimate the risk of bias in meta-analyses and systematic reviews of clinical randomized trials.

Discussion

Treatment's Effect on Pain

The visual analog scale was used to identify pain intensity, the standard method in assessing pain and responses to analgesic treatment because it is simple, reproducible, sensitive, and linear. All studies concluded that analgesics were clinically effective in managing pain in these patients. However, these results should be analyzed with caution since this method may be a source of biases, since patients may be inclined to indicate a greater or lesser degree of satisfaction with their treatment if it is nominative. Arthrocentesis is a minimally invasive surgical technique that essentially rinses the joint by placing needles into the upper joint compartment. Introduced by Nitzan et al. in 1991 [23], this procedure has quickly gained notoriety among practitioners treating TMJ disorders. The use of intra-articular medications after arthrocentesis has gained popularity over the past decade. Several clinical trials have attempted to improve the efficacy of TMJ arthrocentesis by injecting corticosteroids, sodium hyaluronate, platelet-rich plasma, etc. into the joint space.

Experience with arthroscopic procedures on knee joints has shown that intra-articular analgesics can be injected at the end of the procedure to provide early pain relief [24] and has inspired several clinicians to evaluate its use after TMJ arthrocentesis.

The systematic reviews by Siyan Liu and colleagues [25], Venkatesan Gopalakrishnan and colleagues [10] plus the meta-analysis by Yan Liu and colleagues [26]. Also confirmed that intra-articular injection of analgesics had a positive effect on pain reduction after arthrocentesis, considering that the presence of intra-articular opioid receptors located in the synovium makes it possible to obtain a powerful, direct, and lasting analgesic action of the opioids at the affected site, bypassing their central effect.

Ganti S. et al. [15] state that the use of tramadol in pain control began long ago, and over the past four decades, it has been the drug of choice for controlling severe pain disorders [27]. However, the results of their study show that its efficacy is still lower than the combination of glucosamine and chondroitin sulfate. These results seem to agree with those of Damlar I. et al. [28].

Table 1: Description of studies according to PICO criteria.

Route of administration	Author/Year	Population	Intervention	Comparison	Outcomes
Effect of topical analgesic administration	Campbell B.K. et al. 2017 [14]	**-Size:** 70 Subjects **-Sexe:** Female only **-Age:** 18 to 65 years old	**Capsaicin** powder was compounded into an 8% (w/v) topical emollient cream base; **The vehicle cream** was the same topical solution but contained no capsaicin.	Between two groups: **1- Healthy control subjects**: - 30: capsaicin cream - 24: vehicle cream **2- Sick subjects :** - 8: Capsaicin cream - 8: Vehicle cream	**-Experimental and Global Pain:** Significant increase in VAS scores for capsaicin-treated subjects compared to vehicle-treated subjects, the VAS measures during 1 to 7 days were significantly greater in the control vehicle group than in the capsaicin treatment group (P = 0.001). The VAS ratings were significantly lower for the capsaicin-treated subjects over the 1-wk post-application period (P = 0.033). -**Thermal Pain Threshold:** Significant decrease in thermal pain threshold at 2 h after application of the cream in the 2 groups treated with capsaicin, no significant difference in the 2 groups treated with the vehicle cream. **-Pressure Pain Threshold:** No significant change in pressure pain threshold values for all groups.
Effect of oral analgesic administration	Ganti Srivinas et al. 2018 [15]	**-Size:** 60 subjects **-Sexe:** 30 males, 30 females **-Age:** undetermined	Conscious sedation was performed, and Normal saline lavage was performed in the upper joint space. This sample was used to assess the level of IL–6, IL–1ß, TNF–α, and PGE2. Thereafter, each group of patients received the designated test molecule - The same procedure was repeated after **8 weeks** to obtain synovial fluid.	The patients were divided into three groups of 20 each. **Group I** received a combination of 1.5 g of glucosamine and 1.2 g of chondroitin sulfate per day and **group II** received 50 mg tramadol HCL peroral. **Group III** received Sodium hyaluronate 10 mg/ml, 2 ml injection syringe on each joint.	**-Pain VAS score**: Significant decrease in pain in all 3 groups (P<0.05) **-MMO:** Significant increase in MMO in all 3 groups. **-IL-6:** Significant decrease in IL-6 levels in-group I, no significant difference from baseline in groups II and III. **- IL-1β:** - Significant decrease for group I, Significant increase for group II, No significant difference for group III. **-TNF-α:** The difference was not statistically significant in the three groups. **-PGE2:** The difference was not statistically significant in the three groups.
Effect of intramuscular administration of analgesics	Soo-Kyung Kang et al. 2018 [16]	**-Siez:** 51 Subjects **-Sexe:** 27 Males, 24 Females **-Age:** between 20–59 years old.	The dose of morphine used for TMJ treatments ranges from 0.1 mg to 10 mg. A single injection of the test molecule was made over 10 seconds. - At the most painful site of the superficial masseter muscle, - At the level of the trapezius muscle contralateral to the painful masseter, **Follow-up:** 24 and 48 hours after the injection.	5 groups were randomly divided: **-GI:** Masseter saline **-GII:** Morphine 1,5mg masseter **-GIII:** Morphine 5mg masseter **-GIV:** Lidocaine masseter **-GV:** Morphine 5mg trapezium	• **Masseter level:** **- VAS scores:** Statistically significant difference between patients treated with morphine 5mg and those treated with saline. No statistically significant difference between the morphine 5mg group and the lidocaine group. Morphine 1.5mg did not significantly reduce mean scores until after 48 hours, whereas morphine 5mg resulted in an immediate reduction in scores that persisted throughout the observation period. **-PPT:** Aucune différence statistiquement significative entre tous les groupes. **-PPtol:** Overall significant increase in PPtol measures for groups 1, 2, and 3 but not in group 4. No statistically significant difference between the different groups. • **Trapezius level:** Intramuscular injection of 5 mg morphine into the contralateral trapezius did not result in significant changes in VAS, PPT, and PPtol scores measured at the painful masseter muscle.

Effect of intra-articular analgesic administration	El-Gerby Y.M. et al. 2015 [17]	**-Size:** 40 Subjects **-Age:** undetermined	After Preparation of the operative site and collection of synovial fluid aspirate. Hydraulic pressure was created by injecting 2 ml of saline solution, The joint was then washed with 300 to 500 ml of saline solution. In the end, 1 ml of the test molecule was injected. **Follow-up:** after one month	40 patients were divided randomly into two equal groups with chief complaints of limited mouth opening, TMJ pain, and clicking sounds in the TMJ **-GI**: Tramadol **-GII**: sodium hyaluronate	- After one month, there was a significant decrease in IL-6 levels in both groups. there was a statistically significant difference between the two groups: the maximum decrease in IL-6 was observed in patients in group I who received a tramadol injection
	Tamer Hamed A. 2012 [18]	**-Size** 24 subjects **-Sexe**:6 Males,18 Females **-Age:** between 20–59 years old	After the Preparation of the operative site, the auriculotemporal nerve block was performed with 0.5 ml of the local anesthetic solution. Hydraulic pressure was created by injecting 2 ml of saline solution, The joint was then washed with 300 to 500 ml of saline solution. In the end, 1 ml of the test molecule was injected. **Follow-up:** 3 days, 1 month, 6 months	The tested joints were randomly divided into two groups: **-Group I:** injection of 1 ml. of commercially available COX – 2 inhibitors: Groupe I-A: disc displacement with reduction, Group I-B: disc displacement without reduction **-Group II:** Injection of 1 ml. of tramadol hydrochloride: Groupe II-A: disc displacement with reduction, Groupe II-B: disc displacement without reduction	**-VAS scores:** After 3 days, there was no statistically significant difference between the two groups, however, after 1 month and 6 months Group II showed a statistically significantly higher mean percentage decrease in VAS than Group I. **-MMO:** Pre-operatively, after 3 days and after 6 months, Group II showed statistically significantly higher mean MMO than Group I, however, there was no statistically significant difference between the two groups after 1 month. **- Lateral excursion:** Pre-operatively, there was no statistically significant difference between the two groups, however, after 3 days, after 1 month and after 6 months, Group II showed statistically significantly higher mean lateral excursion than Group I. Comparing groups 1-A and 1-B as well as groups 2-A and 2-B, the results showed no statistically significant differences for any of the variables studied
	El-Gerby M et al. 2015 [19]	**-Size:** 40 Subjects **-Age:** undetermined	-After preparation of the operative site, the auriculotemporal nerve block 0.3 to 0.5 ml of an anesthetic solution was injected and then the needle was introduced into the upper joint compartment and approximately 3.5 ml of anesthetic solution was injected. Hydraulic pressure was created by injecting 2 ml of saline solution; The joint was then washed with 300 to 500 ml of saline solution. In the end, 1 ml of the test molecule was injected. **Follow-up:** 3 days, 1 month, 6 months	The selected patients were divided randomly into two equal groups : **Group I:** 20 patients (1ml of tramadol) **Group II:** 20 patients (1ml sodium hyaluronate)	**- Evaluation of Pain**: There was a highly significant reduction in pain score level in both groups as in group I was and in group II **-MMO:** At six months postoperatively: Mouth opening increased significantly in-group I from (17.30 ± 2.85) to (49.80 ± 2.19) and group II from (16.70 ± 3.29) to (38.15 ± 3.54). The difference between the two groups is statistically significant. **-Clicking Sound:** After six months, in the group I clicking was reported at 25 % while in-group II clicking where continuous elevation to 50 %.
	Sipahi A. et al. 2015 [20]	**-Size :** 30 patients **-Sexe** : 25 Females et 5Males **-Age** : between 16–50 years old	After the preparation of the operative site, local anesthesia was obtained with 2%articaine hydrochloride, 0.5-1 ml. A needle was placed in the upper joint space. After distension of the upper compartment with 2 ml of Ringer's lactate, another needle of the same diameter was placed to provide drainage. The joint was irrigated with 60-100 ml of Ringer's lactate, one of the needles was removed, and the study drug was administered through the remaining needle. **Follow-up:** 15min, 1 month, 3 months, 6 months	Patients were randomly divided into 3 groups of 10 each: **-GI** de control: 1ml of 5% Ringer's lactate. **-GII:** 0.01 g Morphine made up to 10 ml with Ringer's lactate **-G III:** 50mg of was mixed with 1 ml of 5% Ringer's lactate.	**-VAS Scores:** Significant decrease in VAS scores during follow-up periods in all groups. Mean VAS scores for pain in mouth opening in the morphine group decreased from (7.3±1.6) to (1.2±0.8) and were significantly lower than those observed in the placebo group during all follow-up periods. In the tramadol group: change from (7.1±1.7) to (.5±1.8); no statistically significant difference from the morphine group. **-MMO:** No significant difference in maximum mouth opening between the different groups.

	Fayed M. et al. 2016 [21]	**-Size:** 40 patients **-Sexe:** 20 F and 20 H **-Age:** between 2°–34 years old	After preparation of the operative site, the auriculotemporal nerve block 0.3 to 0.5 ml of an anesthetic solution, Hydraulic pressure was created by injecting 2 ml of saline solution; The joint was then washed with 300 to 500 ml of saline solution. In the end, 1 ml of the test molecule was injected. **Follow-up:** Immediately after the procedure, at1 week, 3 months, and 6 months.	Between two groups of 20 patients, each randomly divided: Group I: Intra-articular injection of 1ml fentanyl Group II: Intra-articular injection of 1ml of Sodium hyaluronate	**- Pain score:** Preoperatively and immediately, post-operative there was no significant difference between Group I and II. In the following post-operative observation times1week, 1 month, and 6 months; there was a significant difference between both groups ($p < 0.0001$), with higher values, recorded in group II. **-MMO:** Preoperatively and immediately post-operative there was no significant difference between Group I and II. In the following post-operative observation times 1 week, 1 month, and 6 months; there was a significant difference between both groups, with higher values recorded in group I ($p < 0.0001$). **-Mandibular functions**: Preoperatively and immediately post-operative there was no significant difference between Group I and II. In the following post-operative observation times1week, 1 month, and 6 months; there was a greater mean value in group I.
	Al-Kisbi A.M. et al. 2017 [22]	**-Size:** 40 patients **-Sexe:** Females and males	-After the Preparation of the operative site, the auriculotemporal nerve block was performed with 0,3-0,5 ml of the local anesthetic solution. Hydraulic pressure was created by injecting 2 ml of saline solution; The joint was then washed with 200 ml of saline solution. In the end, the test molecule was injected. **Follow-up:** 1 week, then 1, 3, and 6 months after the procedure.	Between two randomly divided groups: -Group I: Butorphanol tartrate, -Group II: Sodium Hyaluronate	**-Pain score:** After 6 months: Statistically significant difference between the two groups; greater reduction in pain score in the group I **-MMO:** Statistically significant difference between the two groups; greater mouth opening was recorded in the group I **-Clicking sound:** After 6 months: Statistically significant difference; more patients reported clicking In-group II.

VAS: Visual analog scale, MMO: Maximum mouth opening, TMJ: Temporomandibular joint.

Table 2: Risk of Bias of the Included Studies.

Study	Randomization	Secret assignment	Blind Procedures	Follow-up	Risk of bias
Ganti Srivinas et al. [15]	Yes (Not clear)	Not clear	Not clear	Yes	Uncertain
Soo-Kyung Kang et al. [16]	Yes (Computer program for generating numbers)	Yes	Oui	Yes	Low
El-Gerby M. et al. [17]	Yes (Not clear)	Not clear	Not clear	Yes	Uncertain
Tamer Hamed A. [18]	Yes (Not clear)	Not clear	Not clear	Yes	Uncertain
El-Gerby M. Et al. [19]	Yes (Not clear)	Not clear	Not clear	Yes	Uncertain
Sipahi A. et Coll. [20]	Yes (Not clear)	Yes	Yes	Yes	Low
Fayed H.T.A. M. et al. [21]	Yes (Not clear)	Not clear	Not clear	Yes	Uncertain
Al- Kibsi Taghreed A.M. et al. [22]	Yes (Not clear)	Not clear	Not clear	Yes	Uncertain
Campbell B.K. et al. [14]	Yes (Random number generation program)	Yes	Yes	2 appropriate exclusions	Low

On another hand, we have Sipahi A. et al. trial [20], whose results showed that the pain scores were lower in the morphine group. This could be explained by the greater analgesic efficiency of morphine compared to tramadol. However, there was no statistically significant difference between these values, which supports the results of Christoph T. et al. [29] who inferred that morphine and tramadol had a similar effect on nociceptive pain although morphine was more potent.

In the study by Kyang SK. et al. [16], morphine was also injected into the trapezius muscle contralateral to the painful masseter to determine whether intramuscular morphine produces analgesic responses via the systemic effect. Furthermore, the high dose of morphine (5 mg) used in this study produced no change in masseter pain and tenderness responses when administered into the remote muscle, ruling out the possibility of systemic effects. This was confirmed by Kapral S. et al. [30] who proved through a clinical trial carried out on 60 patients that the analgesic effect of parenterally administered analgesics is not due to systemic effects.

Through the clinical trial conducted by Campbell and Coll [14], it is possible to stipulate that the use of a co-antalgic has proven its effectiveness in pain management. However, given the leniency of the literature on this topic, it is necessary to explore the effects of a higher dose of topical capsaicin before any conclusions can be drawn about TRPV1 (Transient Receptor Potential Vanilloid type 1) being an effective method of controlling temporomandibular pain and ultimately chronic pain.

Effect of Treatment on Maximal Mouth Opening

Study participants showed a significant increase in this parameter at different follow-up periods compared to the other control groups. These results are in agreement with the fact that pain-free jaw movement showed a notable impact on mouth opening and lateral movements [31].

The results of the meta-analyses by Liu, Siyan, and colleagues [25] and Liu Y. and colleagues [26] were also significantly in favor of opioids for improvement in maximal mouth opening after three and six months of follow-up.

However, despite the significantly greater results in the analgesic group compared with the reference treatment group in the Al Kisbi et al. study, the authors relate this improvement primarily to the fact that the upper joint space lavage reduced inflammatory cells in the joint, widened the joint spaces, and improved mouth opening, and not to the injection of the analgesic. Indeed, the presence of inflammatory cells and inflammatory mediators, including arachidonic acid metabolites and cytokines, has been demonstrated in symptomatic TMJ [32].

Therefore, further clinical trials investigating this variable should be conducted to have a clear conclusion.

Effect of Treatment on Cytokine Levels

Inflammatory cytokines such as prostaglandins, interleukins, and TNF-α are potential regulators of osteoclastogenesis [33]. Increased levels of IL-1ß (Interleukin 1 beta), IL-6 (Interleukin 6), and TNF-α (Tumor Necrosis Factor-Alpha) in synovial fluid, which are important outcomes of inflammation, have been frequently discussed in the literature:

- Kaneyama K. et al. [(34] compared the levels of IL- 1ß, IL-6, and TNF-α measured in TMJ synovial fluid in 55 patients with OA and 5 healthy volunteers. The authors found that the levels of inflammatory mediators were higher in patients with internal derangement compared with healthy individuals.
- In another study by the same authors [35], synovial fluids obtained from 57 patients with the degenerative joint disease were compared with those obtained from 7 healthy individuals. The authors concluded that inflammatory mediators were associated with TMJ abnormalities.
- In a trial of 61 patients with manducatory disorders and 7 healthy patients, Kaneyama K. et al. [36] showed that IL-6 and IL-11 concentrations in synovial fluid were increased when there were bone changes in the condyle. In particular, when IL-6 and IL-11 were detected together, there was a high probability of such bone changes.

In our systematic review, two studies [15,17] had as their objective the analysis of the modification of these inflammatory mediators after administration of analgesics:

- In fact, the study conducted by El Garby M. et al. [17] demonstrated a statistically significant decrease in IL-6 levels after injection of analgesics, greater than that recorded in subjects who received sodium hyaluronate, thus proving its effectiveness in modulating inflammation. The present results are consistent with those of Walker [37] who showed that opioids are fully therapeutic drugs and that they exert their anti-inflammatory effects through changes in cellular activation and cytokine expression. This confirms our original hypothesis and proves the curative and not only the palliative effect of opioids.

In the trial conducted by Ganti S. et al. [15], it was shown that the efficacy of tramadol was lower than that of the combination of glucosamine and chondroitin sulfate, two protein components of cartilage. As such, Damlar I. et al. [28] conclude that the glucosamine-chondroitin combination decreases synovial fluid IL1β and IL6 levels in internal TMJ derangements compared with tramadol, whereas changes in synovial fluid TNF-α and PGE levels do not reach statistical significance between the two groups.

No systematic review has addressed this point, which proves to us the lack of sufficient studies that investigate the effect of analgesics on different mediators of inflammation.

Effect of Treatment on Clicking Sound

In studies conducted by El Gerby M. et al. [19] and Al-Kibsi et al. [22], the authors demonstrated a decrease in the number of patients with clicking sounds after injection of analgesics.

According to El Gerby and Coll [19], the disappearance of the postoperative popping sound was possibly due to the effect of the arthrocentesis procedure, as it dilutes inflammatory mediators and releases adhesion and locking of the disc within the joint, which facilitates the sliding of the disc into the upper compartment, which is evidenced by the increase in mouth opening and jaw movements in the normal range.

This explanation is in agreement with Nitzan et al. [23] who stated that lavage of the upper joint space reduces pain by removing inflammatory mediators from the joint, increasing mandibular mobility by removing intra-articular adhesions, eliminating negative pressure in the joint, reclaiming disc and fossa space and improving disc mobility, which reduces mechanical obstruction caused by the anterior position of the disc and thus the clicking sound.

Moreover, the efficacy of analgesics in the management of manducatory system snapping requires further clinical trials to judge the actual action of these molecules.

Conclusion

The use of analgesics increases the efficacy of treatment by decreasing pain intensity and cytokine levels, through both their analgesic and anti-inflammatory actions. This efficacy is similar for both levels II and III. However, additional long-term clinical studies with a larger sample size are needed to confirm the data collected and to further explore the effect of analgesics in the treatment of TMDs.

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