■ LITERATURE REVIEW

Combined Palliative and Anti-Inflammatory Medications as Treatment of Temporomandibular Joint Disc Displacement Without Reduction: A Systematic Review

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ABSTRACT: The aim of this study was to evaluate the efficacy of self-care combined with anti-inflammatory medications in the treatment of temporomandibular joint (TMJ) pain associated with disc displacement without reduction (DDWOR). A systematic review of randomized clinical trials was done by the authors. The databases searched were Medline (1966 to July 2012); EMBASE (1980 to July 2012); and LILACS (from 1982 to July 2012). The review authors independently assessed trials for eligibility and methodological quality and also extracted all data. The data was double-checked for accuracy. There was no language restriction in the searches of EMBASE, PubMed, and LILACS databases, or in the manual search. The risk of bias and the heterogeneity of the studies taken into consideration were assessed. Two studies, randomizing 175 patients, were included in this review. The first study (n=106) compared the following interventions: medical treatment, rehabilitation, arthroscopic surgery with post-operative rehabilitation, or arthroplastic surgery with post-operative rehabilitation. The second study (n= 69) compared the use of nonsteroidal anti-inflammatory medications and self-care instructions, nonsteroidal anti-inflammatory medications, occlusal splint, and mobilization therapy. The third group received no treatment; patients were only informed of their prognosis. There is no sufficient evidence regarding efficacy and safety of the palliative treatments associated with anti-inflammatory versus other treatments, or absence of treatment on pain reduction in patients with TMJ DDWOR.

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Temporomandibular disorders (TMD) include clinical alterations of the masticatory muscles, the temporomandibular joints (TMJs) and/or associated structures.[1] Epidemiologic studies have estimated that TMJ disorders (TMD) affect over 10 million Americans, and that they seem to be more common in women than in men.[2] Schiffman, et al. analyzed 106 individuals: 8 male and 98 female, and Minakuchi, et al. evaluated 69 patients: 7 male and 62 female, who presented TMJ disc displacement without reduction.[3,4] Data obtained from these studies are in accordance with the prevalence reported by the National Institute of Dental and Craniofacial Research (NIDCR) and the National Institutes of Health (NIH).

An appropriate definition of TMD must include the different signs and symptoms of the condition that would assist in formulating a precise diagnosis. Several classifications have been proposed for this purpose,[1,3] but only two are widely accepted. The first, from the American Academy of Orofacial Pain (AAOP) is regularly used for

clinical practice, while the second, from the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)[5] is used for clinical research in spite of being less inclusive regarding the clinical aspects of the AAOP classification.

Disc displacement without reduction (DDWOR) is described by the AAOP[1] as a misalignment of the articular disc-condylar head structural relationship, which is maintained during mandibular translation, during which the articular disc is not reduced to its regular anatomical position. This clinical condition (DDWOR) can be classified as either acute or chronic.[1]

Acute displacement is characterized by persistent and markedly limited mouth opening (≤35 mm), with a history of sudden onset, deflection to the affected side during mouth opening, sharply limited laterotrusion to the contralateral side (if unilateral); soft tissue imaging indicating displaced articular disc without reduction, and hard tissue imaging revealing no extensive osteoarthritic changes. Chronic displacement is characterized by a history of sudden onset limitation of mouth opening, which occurred more than four months earlier, soft tissue imaging indicating a displaced articular disc without reduction, and hard tissue imaging revealing no extensive osteoarthritic changes.

Once the diagnosis of disc displacement without reduction of the TMJ is established, it is important to determine the optimum intervention for the treatment of the condition.[6-8] Therapeutic possibilities for patients with TMJ pain secondary to DDWOR vary from conservative treatments, such as occlusal splints, physiotherapy, and self-care, to more invasive treatments, such as arthrocentesis, arthroscopy, and open joint surgery of TMJ.[1,9,10] Highlighted are several forms of treatment that offer a favorable prognosis for TMJ DDWOR, including palliative treatment (self-care) combined with anti-inflammatory medications. This treatment is used especially for TMJ pain with this type of disc displacement. The efficacy of this type of intervention has not been widely assessed. The current assessment is performed using a systematic review of the interventions,[11-14] utilizing the Cochrane Collaboration Criteria. The aim was to evaluate the efficacy of self-care[3,4] combined with anti-inflammatory medications for the treatment of temporomandibular joint pain associated with disc displacement without reduction (DDWOR).

Study Design: Systematic Review of Randomized Controlled Trials

For the assessment of study quality, the Cochrane Collaboration's tool for assessing risk of bias was followed.[15,16] The following six criteria were used:

1. **Random sequence generation**: Allocation sequence should be adequately generated, for example with random number tables or computer-generated random numbers. The authors recorded this as *low risk of bias* when the method used was either adequate or unlikely to introduce bias; as *uncertain risk of bias* when there was insufficient information to assess whether the method used was likely to introduce bias; or as *high risk of bias* when the method used (e.g., quasi-randomized trials) was improper and likely to introduce bias.

2. **Allocation concealment**: Allocation should be adequately concealed in a way that does not allow either the investigators or the participants to know or influence allocation to an intervention group before an eligible participant is entered into the study (e.g., using central randomization or sequentially numbered, opaque, sealed envelopes held by a third party). The authors recorded this as *low risk of bias* when the method used (e.g., central allocation) was unlikely to introduce bias in the final observed effect; as *uncertain risk of bias* when there was insufficient information to assess whether the method used is likely to introduce bias in the estimation of the effect; or as *high risk of bias* when the method used (e.g., open random allocation schedule) was likely to introduce bias in the final observed effect.

3. **Blinding**: The authors recorded blinding of assessors as *low risk of bias* if blinding was performed adequately, or the outcome measurement was not likely to be influenced by lack of blinding; and as *uncertain risk of bias* if there was insufficient information to assess whether the type of blinding used was likely to induce bias in the estimation of the effect; or *high risk of bias* if there was no blinding or incomplete blinding, and the outcome or the outcome measurement was likely to be influenced by lack of blinding.

4. **Incomplete outcome data**: Incomplete outcome data was adequately addressed. Incomplete outcome data essentially included: attrition, exclusions, and missing data. If any withdrawals occurred, they were described and reported by treatment group, with reasons given. The authors recorded whether or not there were clear explanations for withdrawals and dropouts in the treatment groups. An example of an adequate method to address incomplete outcome data is the use of an intention-to-treat (ITT) analysis. This item was recorded as *low risk of bias* when the underlying reasons for missing data were unlikely to make treatment effects depart from plausible values, or when proper methods were employed to handle missing data. The authors recorded as *uncertain risk of bias* when there was insufficient information to assess whether the missing data mechanism, in combination with the method used to handle missing data, was likely

to induce bias in the estimation of the effect; and as *high risk of bias* when the crude estimate of effects (e.g., complete case estimate) was clearly biased due to the underlying reasons for missing data, and the methods used to handle missing data are unsatisfactory.

5. **Selective reporting**: The reports of the study should be free from any suggestion of selective outcome reporting. This was interpreted as there being no evidence that statistically nonsignificant results might have been selectively withheld from publication; e.g., selective underreporting of data or selective reporting of a subset of data. The authors recorded this as *low risk of bias* when the trial protocol was available and all of the trial's prespecified outcomes that were of interest to the review were reported. The authors recorded as *uncertain risk of bias* when there was insufficient information to assess whether the magnitude and direction of the observed effect was related to selective outcome reporting; or as *high risk of bias* when not all of the trial's prespecified primary outcomes were reported.

6. **Other bias** (e.g., conflict of interests): Initially, the authors copied the information considered relevant for making a judgment on the criteria from the original publication into an assessment table. Two review authors made their own independent judgments as to whether the risk of bias for each criteria was considered to be *low*, *uncertain*, or *high*. The authors resolved any disagreements by discussion, and considered only the trials which were classified as *low risk of bias*, taking into consideration the following criteria: sequence generation, allocation concealment, blinding, incomplete data, and selective outcome reporting as low bias risk trials (**Tables 1** and **2**).

Materials and Methods

Search and Selection Strategies

A systematic search of the literature was performed on randomized or quasi-randomized multiple databases reporting a) effects of palliative treatments combined with anti-inflammatory medications, and b) subjects over 18 years old presenting clinical diagnoses of disc displacement without TMJ reduction using the following databases: CENTRAL (2012, 3rd ed.), PubMed (from 1966 to July 2012), EMBASE (from 1980 to July 2012) and LILACS (from 1982 to July 2012). Available published and unpublished studies were researched according to the dates given above in each of the database platforms up to July 2012. The search was conducted using multiple combinations of the following keywords: palliative care, temporomandibular joint dysfunction, disc displacement without reduction, and controlled clinical trials. A manual bibliographic search for selected articles and of primary dental journals was also performed.

There were no restrictions concerning language and geographic location. A search strategy (**Table 2**) was utilized to study type identification (i.e., clinical trials) for clinical situations and interventions of interest. A manual search for clinical trial references was performed in relevant journals. Email contact was used to obtain additional information from the authors, and specialists in the area were contacted in an attempt to identify unpublished studies.

Search Strategy Used to Identify Type of Study in the Databases, EMBASE, PubMed and LILACS (i.e., Clinical Trials) for the Type of Clinical Situation and Intervention

Selection of studies: Two reviewers independently assessed all the studies identified to determine whether they met the predefined inclusion criteria. All the references mentioned in the 229 articles identified in the search were reviewed and included if they met the criteria. The reasons for excluding a study were documented. A third independent reviewer resolved any differences that arose as to whether a trial should be included or not.

Data extraction and management: Two independent reviewers examined studies that fulfilled the inclusion criteria in detail. The two reviewers extracted the following data using a standardized data extraction form: characteristics of the study (design, randomization method, etc.); participants; interventions; clinical outcomes (types of measured outcomes, i.e., dichotomic or continuous; adverse effects). The form was based on the Cochrane Handbook (**Table 1**).

Assessment of risk of bias in the included studies: The following parameters were assessed: method and/or security of randomization; whether or not the individuals involved in the study (including health care provider, assessor, and patient) were blinded to the treatment allocation; whether analysis by intention-to-treat was performed; and how many participants completed the study.

Any differences in interpretation of the data were resolved through consensus among the reviewers. If additional information was required, an attempt to contact the original authors of the study was made.

Study Selection

Abstracts of the results of electronic searches were evaluated by two independent researchers for the selection of those articles that were potentially related to this work. When an abstract was not adequate to describe the study design, definition, or application of the selection criteria, the full article was obtained and evaluated by the researchers.

Table 1
Characteristics of the Included Articles and Their Risk of Bias:
Performed According to the Cochrane Handbook of Intervention Systematic Reviews

Study Id.: Schiffman, 2007[3]		
Method	**Participants**	**Intervention**
Design: RCT Single-center **Period**: June 1992 to June 2004 **Sample size**: reported **Intention-to-treat analysis**: used **Follow-up**: 60 months	**Number**: 106 patients **Gender**: 92.7% female **Age**: (average) per experimental group: a. medical treatment, 33.7 yrs.; b. rehabilitation, 30 yrs.; c. arthroscopic surgery, 31.8 yrs.; and d. arthroplasty, 31.4 yrs. **Site of the study**: University of Minnesota, EUA **Inclusion criteria**: age, 18 to 65 yrs.; daily complaint of pain in the joints related to the movement of the mandible and its functioning; report of pain during the joint examination; diagnosis by MRI, stage III or IV (closed lock), limited mouth opening; and being available for at least two years. **Exclusion criteria**: evaluated by the medical records, including: systemic rheumatologic disease; generalized articular pain or swelling; pregnancy; concomitant use of corticosteroids, anti-inflammatory, muscle relaxants, or narcotics; severe psychiatric disease; another medical contraindication.	Patients were randomly divided into four groups: **a**. medical treatment; **b**. rehabilitation; **c**. arthroscopic surgery with post-operative rehabilitation, or **d**. arthroplasty with post-operative rehabilitation

	Bias risk assessment		
Outcomes evaluated	**Item**	**Judgement**	**Description**
Mandibular function and TMJ pain as primary outcomes measured by CMI and SSI scales, respectively.	Was the allocation generation performed?	Moderate bias risk	Not reported (stratified)
	Was the allocation concealment performed?	High bias risk	There was allocation concealment related to the participants and the ones who helped in the study until the end of recruiting. However, after that, the coordinator of the study opened the envelopes and informed the participants about the allocation of the groups.
	Was the control of incomplete data checked?	Moderate bias risk	9.43% loss and abandonment rate from the total sample, but it was not clear if there was a substantial difference between the groups. The authors used the intention-to-treat analysis.
	Was it free of selective reporting of outcomes?	Low bias risk	No recognizable bias.
	Were the relevant outcomes evaluated?	Low bias risk	Mandibular function and TMJ as the primary outcome measured by CMI and SSI scales, respectively.
	Were the outcomes evaluated by a "blind" researcher for the allocation group?	Low bias risk	Yes.

(Table 1 cont. on next page)

Risk of Bias Evaluation

Evaluation of risk bias was made utilizing the Cochrane Handbook risk of bias table.[15] Studies were classified as presenting high, uncertain, or mild risk of bias, according to evaluation of the following items: generation of allocation sequence, allocation concealment, blinding, adequate incomplete data description, the presence of reporting bias, and other sources of bias that might influence the validity of the study.

Table 1 (cont.)
Characteristics of the Included Articles and Their Risk of Bias:
Performed According to the Cochrane Handbook of Intervention Systematic Reviews

Study Id.: Minakuchi, 2004[4]		
Method	**Participants**	**Intervention**
Design: RCT Single-center **Period**: March 1997 to July 1998 **Sample size**: not reported **Intention-to-treat analysis**: used **Follow-up**: 8 weeks	**Number**: 69 patients **Gender**: 7 males and 62 females **Age**: 34.0 yrs. **Site of the study**: Okayama University Dental Hospital, Japan **Inclusion criteria**: the eligible individuals were the ones who reported pain in the TMJ of the displaced disc without reduction and were selected according to the following criteria: 1. report of pain on mouth opening, masticatory difficulty, or both; 2. mouth opening in the area of TMJ at a level of more than 10/100 mm, according to a VAS pain scale; 3. a positive diagnosis of TMJ pain or disc displacement without reduction found on MRI, according to the IZ operational criteria. **Exclusion criteria**: the subjects were excluded if they presented one or more of the following conditions: 1. were not willing or could not attend all the monitoring visits; 2. were edentulous; 3. had a severe systemic disease; or 4. had or were submitted to some kind of dental or TMJ treatment (i.e., use of medication or therapy with intraoral appliance) in other clinics.	Participants were randomly divided into three experimental groups: **a**. group 1 made use of non-; steroidal anti-inflammatory and self-care instructions (group of palliative care). **b**. group 2, nonsteroidal anti-inflammatory, self-care instructions, occlusal appliance, and mobilization therapy (physiotherapy group), and **c**. group 3, did not receive treatment (control group). Individuals were also instructed about self-care, use of hot or cold compresses, soft-food diet, and gentle exercises for mouth opening.

	Bias risk assessment		
Outcomes evaluated	**Item**	**Judgement**	**Description**
The interventions were evaluated by means of a questionnaire that evaluated: 1. symptom improvement; 2. difficulty in the treatment; and 3. satisfaction with the treatment within the period of 8 weeks.	Was the allocation generation performed?	Low bias risk	Used a computer program to generate randomized numbers.
	Was the allocation concealment performed?	High bias risk	The procedure was performed by the main researcher.
	Was the control of incomplete data checked?	Low bias risk	.8% loss and abandonment rate from the total sample; however, it was not clear if there was a substantial difference between the groups (2 patients, who presented persistent and severe TMJ pain were submitted to arthrocentesis and considered as a loss). The authors used the intention-to-treat analysis.
	Was it free of selected reporting of outcomes?	Low bias risk	No recognizable bias.
	Were the relevant outcomes evaluated?	Low bias risk	Questionnaire evaluated: 1.symptom improvement; 2. difficulty in treatment; and 3. satisfaction with treatment.
	Were the outcomes evaluated by a "blind" researcher for the allocation group?	Low bias risk	Not reported

Table 2
Search Strategy for Type of Clinical Situation and Intervention

Search terms used
[(Palliative Care) OR (Palliative Therapy) OR (Palliative Treatment) OR (Palliative Treatments) OR (Palliative Surgery) OR (Palliative Medicine) OR (Home Care)) AND ((Disk Herniated) OR (Disks Herniated) OR (Herniated Disk) OR (Herniated Disks) OR (Slipped Disk) OR (Disk Slipped) OR (Disks Slipped) OR (Slipped Disks) OR (Disk Prolapse) OR (Disk Prolapses) OR (Prolapse Disk) OR (Prolapses Disk) OR (Prolapsed Disk) OR (Disk Prolapsed) OR (Disks Prolapsed) OR (Prolapsed Disks) OR (Herniated Disc) OR (Disc Herniated) OR (Discs Herniated) OR (Herniated Discs) OR (disc displacement) OR (Closed lock) OR (displacement without reduction)]

Statistical Analysis

Statistical analysis was carried out using Review Manager Ver. 5.3.[16] For the dichotomous variables, risk ratio (RR) was utilized with a 95% confidence interval, applying a fixed effects model. Sensibility and subgroup analyses were performed when possible.

Interventions

Considered interventions included palliative treatment combined with anti-inflammatory medications versus other interventions, such as: a) behavioral, (recommendations concerning several factors that can trigger pain, such as stress and lack of sleep); b) educational (information on mechanisms of pain); c) pharmacological (tricyclic antidepressants, analgesics, muscle relaxants, and nonsteroidal anti-inflammatory); d) alternative therapies (acupuncture and physiotherapy); e) combination therapy (palliative treatments associated to steroidal and nonsteroidal anti-inflammatory, occlusal appliance, and articular mobilization); and f) no intervention.

Outcomes

Primary evaluated outcomes were: a) frequency; b) intensity; and c) duration of pain events using instruments, such as the visual analog scale (VAS), categorical scales, or other [Craniomandibular Index (CMI) and modified Symptom Severity Index (SSI)]; d) symptom remission was measured by self-report. Secondary outcomes were: a) measured quality of life (SF-36 and/or OHRQoL); b) adverse effects (diffuse gastritis, nausea, vomiting, gastric bleeding, dyspepsia, allergies, hives, renal failure hemorrhage); c) depressive disorders; d) anxiety; e) sleep disturbances; f) discontinuation of treatment; g) number of patients that required muscle relaxants and analgesics; h) exclusion of duplicated publication of the same study (original study, animal research, case reports and literature reviews).

Data extraction and Quality Assessment

A tool for assessing bias risk was utilized (form based on Cochrane Handbook) to evaluate methodological quality of clinical findings.[11-14]

Two researchers reviewed titles and abstracts to identify potential articles. Documents were obtained and entirely evaluated by two reviewers independently. Disagreements were resolved by discussion and, when necessary, a third reviewer was contacted. Grounds for exclusion were identified. Data extraction was carried out based on inclusionary or exclusionary criteria as defined above. For dichotomous data, risk ratio (RR) was used as an effect measure.

Results

Studies Selection

The electronic search returned a total of 229 publications from electronic databases, and they were evaluated utilizing titles and abstracts of each article. After examining titles and abstracts, the authors obtained two complete copies of two eligible articles.[3,4] The other 227 did not meet the requirements of this study or were unacceptable narrative reviews. Manual searches did not return any additional studies to be included, (**Figures 1** and **2**).

The included studies, Schiffman, et al. and Minakuchi, et al.,[3,4] discussed a total of 175 patients (15 male and 160 female) ages between 18 and 65, with disc displacement without TMJ reduction as confirmed by magnetic resonance imaging. Schiffman[3] assessed more subjects (n=106; 60.57%), while Minakuchi[4] investigated fewer patients (n=69; 39.42%).

Schiffman[3] examined 106 individuals, 92.7% female with an average age of 31.7 during a 60-month period, and Minakuchi[4] evaluated 69 patients, 7 men and 62 women, average age of 34.0 years, during an eight-week period (**Table 3**).

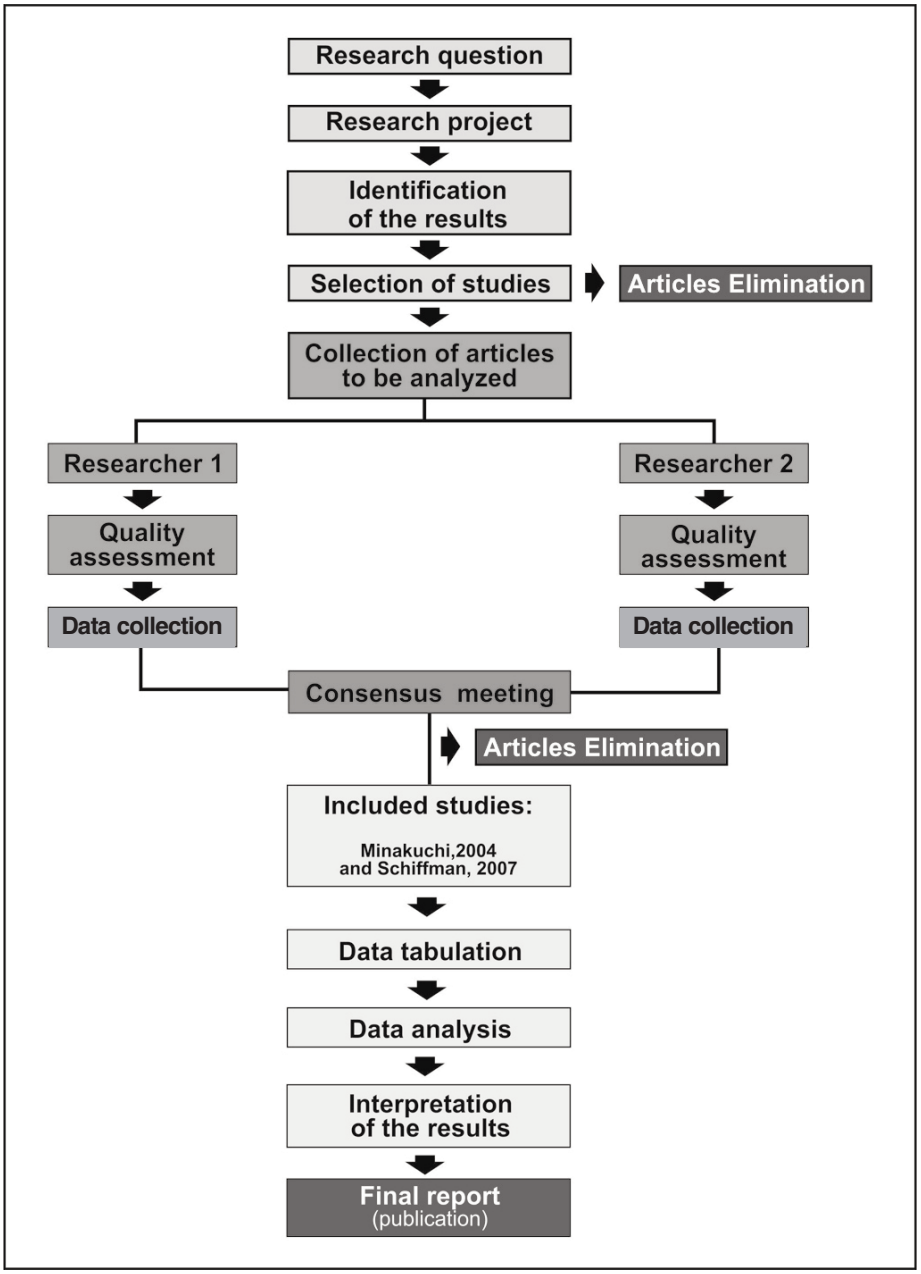

Figure 1
Flowchart explaining the different steps performed in the systemic review strategy (adapted from Ross, et al.: Systemic review of literature regarding the diagnosis of sleep apnea. *Evidence report number 1* (Contact 290-97-0016 to Metaworks, Inc.) Rockville, MD: Agency for Health Care Policy and Research, February 1999.

Subjects from the Schiffman[3] study were randomized into four groups: a) medical treatment, b) rehabilitation, c) arthroscopic surgery with post-operative rehabilitation or d) arthroplasty with post-operative rehabilitation.

Medical treatment included counseling regarding the patient's condition, a self-help program and a six-day regime of oral methylprednisolone combined with nonsteroidal anti-inflammatory medications for 3-6 weeks. When necessary, muscle relaxants were used.

Rehabilitation included treatment performed by a dentist, physiotherapist, and psychologist. Participants were randomly assigned to one of the two treatments: a) medical treatment (as previously described) combined with an oral appliance (occlusal splint), physiotherapy, and cognitive behavioral therapy.

Physiotherapy consisted of articular mobilization, physiotherapeutic modalities, and a home exercise program.

Cognitive behavioral therapy included oral habits evaluation, psychopathology, and two follow-up sessions focusing on education, reversal of habits, and improving adherence to treatment and self-efficacy.

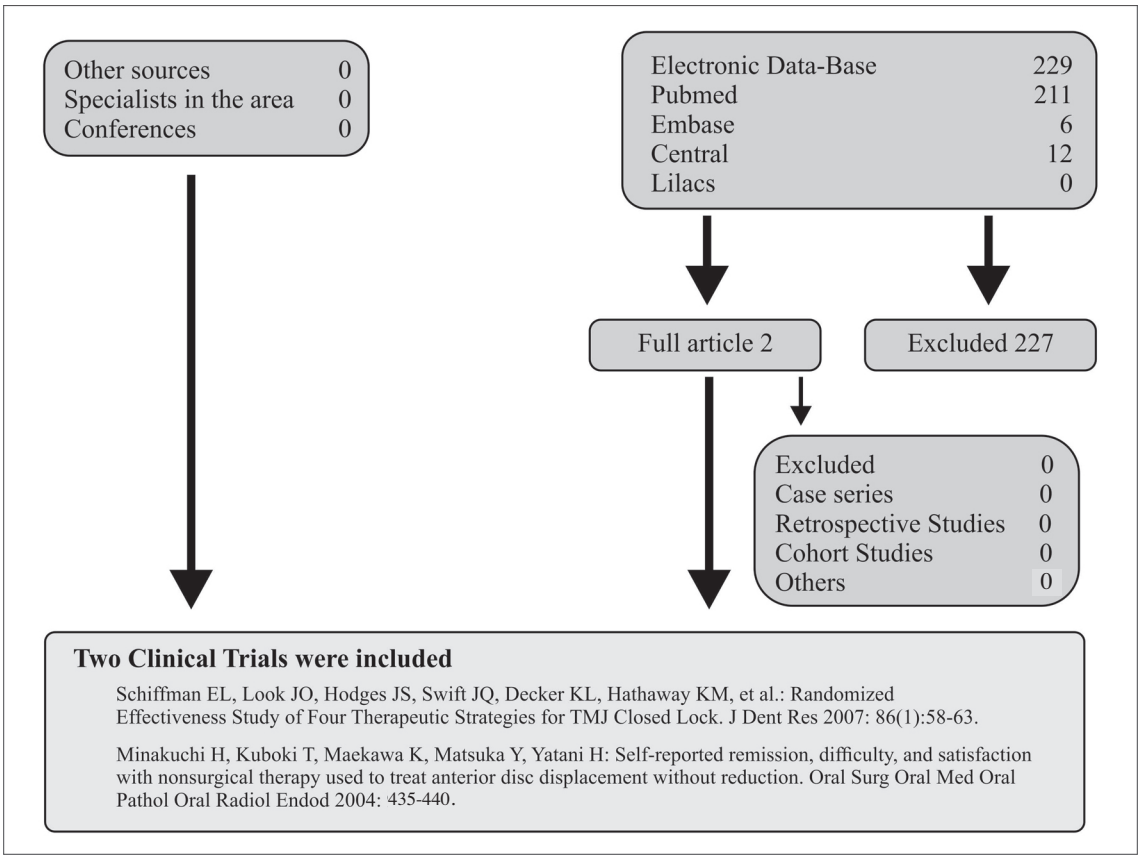

Figure 2
Flowchart of the studies included and excluded in the systematic review.

Arthroscopy was performed by a maxillofacial surgeon under general anesthesia. The superior joint space was lavaged, and intracapsular betamethasone was injected. The success of this treatment was evaluated when the joint was manually moved by excursive movements.

Arthroplasty was performed by a maxillofacial surgeon under general anesthesia. There was an attempt to reposition the disc. Discs with advanced degenerative changes were removed (discectomy).

Minakuchi[4] divided patients into three groups: a) group 1 consisted of subjects treated with a nonsteroidal anti-inflammatory for a four-week period who were instructed in self-care (palliative treatment groups); b) group 2 consisted of subjects treated with a nonsteroidal anti-inflammatory, self-care instructions, occlusal splint, and mobilization therapy (physical therapy group); c) group 3 consisted of no treatment (no intervention, considered as the control group). The follow-up and observation period of this study was eight weeks.

The control group received only information regarding the prognosis. Subjects from group 1 (palliative care) received diclofenac sodium (nonsteroidal anti-inflammatory) prescribed three times per day in doses of 25 mg, (Ciba-Geigy, Tokyo, Japan), and also a grastroprotective agent (Isalon Granules, Takeda, Osaka, Japan) prescribed three times per day in doses of 600 mg.

Participants in the Minakuchi[4] study were also instructed regarding self-care, which consisted of the utilization of hot or cold compresses, a soft diet, and mild mouth-opening exercises. Group 2 patients' (physiotherapy) treatment included an occlusal splint (stabilization or flat) and active mobilization therapy of the jaw, as well as the same therapies offered to patients included in the palliative treatment group.

Schiffman[3] evaluated mandibular function and TMJ pain as primary outcome measures, respectively by CMI and SSI. Minakuchi[4] assessed the improvement of jaw mobility, patient satisfaction, and difficulties with treatment, using a questionnaire (Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods) (**Table 4**).

Table 3
Characteristics of the Clinical Trials

Patients	Interventions	Results
	Study Id.: Schiffman, 2007[3]	
n = 106 (8 male, 98 female)	Patients were randomized into four groups: a. medical treatment; b. rehabilitation; c. arthroscopic surgery with post-operative rehabilitation; or d. arthroplasty with post-; operative rehabilitation.	There was a significant statistical difference in the patients receiving rehabilitation treatment; in other words, the patients from the palliative group treated with an anti-inflammatory required analgesics more than once per week when compared to patients in the rehabilitation group. There was a significant statistical difference in the patients who underwent arthroplasty, in other words, the patients from the palliative group treated with anti-inflammatory required more analgesics, more than once per week, when compared to the patients of the arthroplasty group. There was a significant statistical difference toward the patients receiving rehabilitation treatment; in other words, the patients who underwent arthroscopic surgery required more analgesics, more than once per week, when compared to the patients of the rehabilitation group. There was a statistical significant difference in the patients who underwent arthroplasty, compared to the ones who underwent arthroscopic surgery, regarding the prescription of more than one analgesic per week.
	Study Id.: Minakuchi, 2004[4]	
n = 69 (7 male, 62 female)	Subjects were allocated into three groups: a. group 1, non-steroidal anti-inflammatory for short period and self-care instructions (palliative treatment group); group 2, non-steroidal anti-inflammatory, self-care instructions, occlusal splint, and mobilization therapy (physical therapy group); c. group 3, no treatment (no intervention, control group). The individuals in this study were instructed regarding self-care: the use of cold or hot compresses, soft-food diet, and instructed to perform gentle exercises for mouth opening. Follow-up and observation period of this study was 8 weeks.	Improvement scores in the palliative care group were significantly better than those in the physical medicine group or the no-treatment group. Satisfaction scores showed no significant difference among the three groups. The difficulty of the treatment for the physical therapy group was significantly greater than that for the other two groups.

Assessment of the Studies' Quality

The study of Schiffman[3] reported no information concerning the selection process of the subjects, although the authors reported that this process was blinded until the end of recruitment, when the subjects were informed of their group assignments. Since allocation was blinded only until the end of the recruitment period, the study was considered inadequate with respect to the randomization process, and classified as presenting high risk of bias.

Moreover, Minakuchi[4] utilized a computer method to generate random numbers, and was classified as presenting low risk of bias. On the subject of blinding, allocation was performed by the main investigator; therefore, the study was classified as inadequate (high risk of bias).

The study developed by Schiffman[3] reported the study as being single-blind, in which only one researcher was blinded regarding treatment allocation during assessment of clinical outcomes. It was also reported that to make participants "blinded" to the surgical treatment group, they should be submitted to a method referred as *sham surgery*. Thus, and considering that in surgical interventions the blinding of the outcomes appraiser is considered adequate, the study was classified as presenting a low risk of bias.

Minakuchi[4] provided no information about blinding methods; therefore, this study was classified as an uncertain risk of bias.

In the study performed by Schiffman,[3,] 10 subjects withdrew from the study after randomization, but before receiving treatment. Of the total sample, eight were evaluated after five years and were included in a more recent analysis. This corresponds to only 9.43% of the

Table 4
Description of Each of the Interventions and Their Respective Study

Interventions	Description of intervention
	Study Id.: Schiffman, 2007[3]
Medical treatment	Instruction regarding the displacement of the disc without reduction of the temporomandibular joint, counseling, self-care program, use of oral methylprednisolone for six days, followed by a nonsteroidal anti-inflammatory for three to six weeks. Muscle relaxants and analgesics were used according to the need of each patient.
Rehabilitation	Medical treatment (described above) combined with intraoral splint, physiotherapy (joint mobilization, physiotherapeutic modalities and a program of exercises to be executed at home) and Cognitive-Behavioral Therapy (evaluation of harmful oral habits, psychological interview, two follow-up sessions focused on education to avoid bad habits and to improve treatment adherence).
Arthroscopic surgery with post-operative rehabilitation	An oral surgeon was chosen at random, and the patient was put under general anesthesia. The upper articular space was washed and betamethasone injected. The success of the treatment was evaluated by the manual excursion of the mandible.
Arthroplasty with post-operative rehabilitation	The intervention was performed by an oral surgeon with the patient under general anesthesia. There was an attempt to repositioned the disc. The disc was removed because the tissue was too degenerated.
	Study Id.: Minakuchi, 2004[4]
Group 1: Palliative care	Use of a nonsteroidal anti-inflammatory (25 mg sodium diclofenac 3 times a day, and a 600 mg gastroprotective agent to be also taken 3 times a day) and self-care instructions (the use of cold or hot compresses, soft food diet, and instruction to perform gentle exercises of mouth opening).
Group 2: Physiotherapy	Use of a nonsteroidal anti-inflammatory, self-care instructions (the use of a cold or hot bag, soft-food diet, and instruction to perform gentle exercises of mouth opening), occlusal splint and mandible mobilization therapy, and the same therapies offered to group 1's patients (palliative care).
Group 3: Control	No treatment. Received only instructions regarding prognosis.

total sample study and was classified as presenting low bias risk. Only two patients from the Minakuchi[4] study required arthrocentesis (2.8%); therefore, it was classified as a low bias risk. (**Figure 3**, **Table 1**)

Effectiveness of the Interventions - Meta-Analysis

It was not possible to accomplish the meta-analyses assembling both studies' findings, because the results in Minakuchi[4] were all presented by median and confidence intervals. There was communication with the authors of that study, requesting data, such as average and standard deviation, to perform additional analyses. They did not reply to the request. Therefore, the following data is based on Schiffman.[3] With respect to the proportion of subjects requiring analgesics more than once per week, there was a statistically significant difference among the groups in the following comparison:

- There was a statistically significant difference regarding the patients receiving rehabilitation treatment, i.e., patients of the palliative group treated with anti-inflammatory medications required more analgesics, more than once per week, when compared to the patients of the rehabilitation group (Relative Risk (RR) 6.38 [Confidence Interval (CI) 95% 1.65, 24.63]);
- There was a statistically significant difference regarding the patients who underwent arthroplasty, i.e., the patients from the palliative group treated with anti-inflammatory drugs required more analgesics, more than once per week, when compared to the patients of the arthroplasty group (RR 11.54 [CI 95% 1.67, 79.54]);
- There was a statistically significant difference regarding the patients receiving rehabilitation treatment, i.e., the patients who underwent arthroscopic surgery required more analgesics, more than once per week, when compared to the patients of the rehabilitation group (RR 0.23 [CI 95% 0.06, 0.95]);
- There was a statistically significant difference regarding the patients who underwent arthroplasty compared to the ones who underwent arthroscopic surgery with regard to the prescription of more than one analgesic per week (RR 7.77 [CI 95% -1.08, 55.89) (**Tables 5**, **6**, **7**, and **8**). Statistically

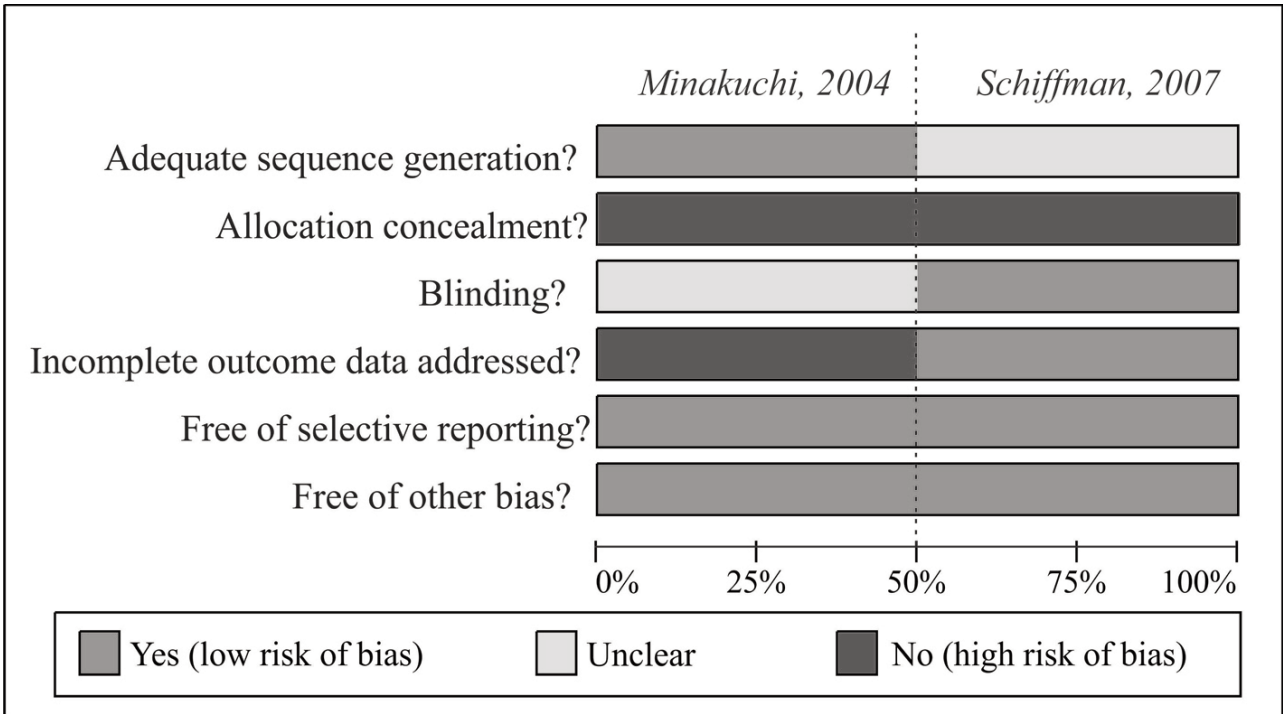

Figure 3
Bar graph showing a review of assessment for each item by percentage of all included studies.

significant differences between groups of other outcomes evaluated were not found.

Discussion

The preset systematic review provides some evidence that was based on two moderate risk of bias studies (clinical trials), regarding the effects of palliative treatments combined with anti-inflammatory medications to treat TMJ pain with chronic and acute disc displacement without reduction.

Schiffman[3] described the first randomized clinical trial that assessed the efficacy of four treatment strategies. Strategies were: medical treatment, rehabilitation, arthroscopic surgery with post-operative rehabilitation, arthroplasty with post-operative rehabilitation, and arthroplasty. The null hypothesis of the study was that there is no difference in the improvement of pain and mandibular function with medical treatment and initial rehabilitation treatment, with or without surgery. Minakuchi[4] conducted a randomized clinical trial in which patients were allocated into three groups: palliative care, physical therapy, and control group.

It was not possible to perform a meta-analysis because the data from the Minakuchi[4] study was insufficient. There was no statistically significant difference related to the primary outcome (frequency, intensity, and duration of pain and mandibular function). There was a statistically significant difference in favor of subjects who required the use of analgesics more than once per week when compared to patients from the medical treatment and arthroscopic surgery group. These findings are reinforced by the methodological quality of this study that included an adequate description of the clinical findings, exhaustive search of electronic databases, and manual searches. This was also supported by the identification, selection, and extraction of data from studies provided independently by two reviewers who critically assessed articles for potential inclusion. Despite this, the present review is limited due to the lack of adequate evidence to formulate decisions on clinical practice.

Despite the limited evidence found in literature, it must be considered that invasive therapy should be performed only after conservative treatments have failed, with the objective of restoring TMJ biomechanics. Conservative treatment is recommended, since the etiology of TMD remains uncertain and has a multifactorial character. Furthermore, the interrelation between risk factors, aggravating factors, and perpetuating factors are not yet well defined, and many cases are complex.[17-19]

Among the conservative treatments available today, splint therapy should be considered, as moderate-quality

Study or Subgroup	Medical Management (palliative treatment + AI) Events	Total	Rehabilitation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schiffman, 2007	17	28	2	21	100.0%	6.38 (1.65, 24.63)
Total (95% CI)		28		21	100.0%	6.38 (1.65, 24.63)
Total Events	17		2			

Heterogeneity. Not applicable

Test for overall effect Z = 2.69 (P= 0.007)

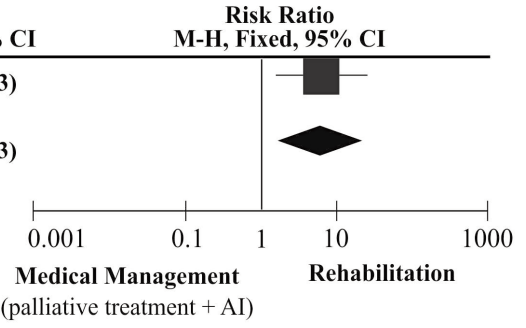

Table 5
There was a statistically significant difference regarding the patients receiving rehabilitation treatment, i.e., patients of the palliative group treated with an anti-inflammatory required more analgesics, more than once per week, when compared to the patients of the rehabilitation group (Relative Risk (RR) 6.38 [Confidence Interval (CI) 95% 1.65, 24.63]).

Study or Subgroup	Medical Management (palliative treatment + AI) Events	Total	Arthroplasty Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schiffman, 2007	17	28	1	19	100.0%	11.54 (1.67, 79.54)
Total (95% CI)		28		19	100.0%	11.54 (1.67, 79.54)
Total Events	17		1			

Heterogeneity: Not applicable

Test for overall effect Z = 2.48 (P= 0.01)

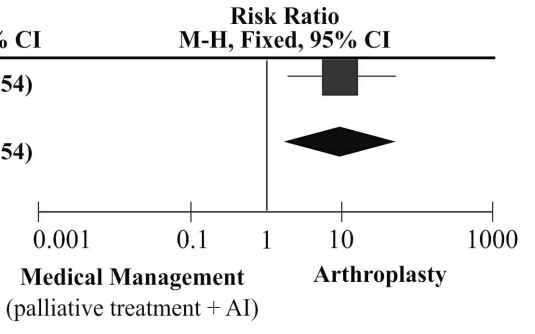

Table 6
There was a statistically significant difference regarding the patients who underwent arthrosplasty, i.e., the patients from the palliative group treated with an anti-inflammatory required more analgesics, more than once per week, when compared to the patients of the arthrosplasty group (RR 11.54 [CI 95% 1.67, 79.54]) in Schiffman.[3]

Study or Subgroup	Rehabilitation Events	Rehabilitation Total	Arthroscopic surgery Events	Arthroscopic surgery Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schiffman, 2007	2	21	9	22	100.0%	0.23 (0.06, 0.95)
Total (95% CI)		21		22	100.0%	0.23 (0.06, 0.95)
Total Events	2		9			

Heterogeneity: Not applicable

Test for overall effect Z = 2.03 (P= 0.04)

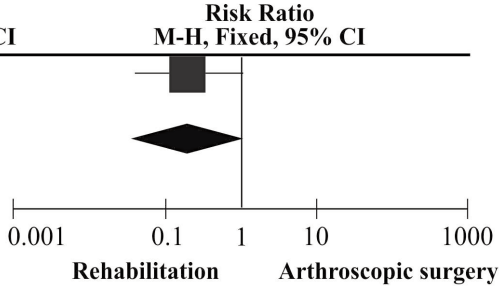

Table 7
There was a statistically significant difference regarding the patients receiving rehabilitation treatment, i.e., the patients who underwent arthroscopic surgery required more analgesics, more than once per week, when compared to the patients of the rehabilitation group (RR 0.23 [CI 95% 0.06, 0.95]) in Schiffman.[3]

Study or Subgroup	Arthroscopic surgery Events	Arthroscopic surgery Total	Arthroplasty Events	Arthroplasty Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schiffman, 2007	9	22	1	19	100.0%	7.77 (1.08, 55.89)
Total (95% CI)		22		19	100.0%	7.77 (1.08, 55.89)
Total Events	9		1			

Heterogeneity: Not applicable

Test for overall effect Z = 2.04 (P= 0.04)

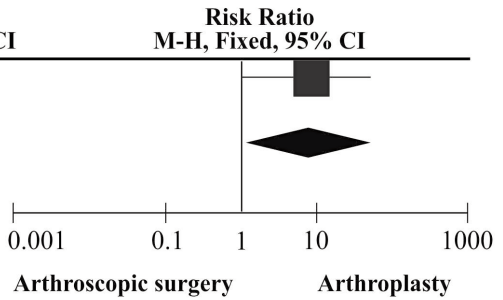

Table 8
There was a statistically significant difference regarding the patients who underwent arthroplasty compared to the ones who underwent arthroscopic surgery with regard to the prescription of more than one analgesic per week (RR 7.77 [CI 95% -1.08, 55.89]) in Schiffman.[3]

evidence suggests that splint therapy may help in the reduction of pain in the temporomandibular joint.[20] This systematic review evaluated the use of splint therapy in adults with TMD. The authors searched the literature published through 2011 in the main electronic databases, and 11 studies were included in the meta-analysis. Their results showed a reduction in the pain within the patients who received splint therapy compared to minimal or no treatment (SMD = -0.93; 95% CI, -1.33 to -0.53). There were no statistically significance differences regarding quality of life and depressive symptoms in either studied group (SMD = -0.09; 95%CI, -0.51 to 0.32; two trials plotted) and (SMD = -0.20; 95% CI, -1.75 to 1.35, two trials plotted), respectively. Although little effect is shown by the splint therapy, the authors suggested further research to confirm the effect of splint therapy in patients with TMD.[20]

Further studies, as the aforementioned, should be conducted in the future, as the main objective of treatment should be pain control. However, there must be adequate, carefully provided instructions to the patient regarding the importance of reducing function during the treatment period, avoiding overloaded functional movements, to allow the injured tissues to recover.[21] When it is established that an invasive treatment is necessary, treatment must prioritize the least invasive or the most minimally invasive procedures first, such as infiltration of medicines and arthrocentesis, which are well-documented and present good quality evidence.[9,10,22-29] However, there are no RCTs for all treatment modalities, and there are several methodological failures in the existing studies. Care must be exercised not to refer to inadequate studies as the basis for clinical decisions.

Implications for Research

There is an urgent need for randomized studies to prove or contest the efficacy of palliative treatments combined with anti-inflammatory medications *versus* other treatments or lack of treatment for the treatment of pain associated with TMJ DDWOR. Future studies must use increased statistical power in order to improve the predictive treatment outcome for patients and subgroups of patients presenting chronic or acute TMJ disc displacement without reduction. Outcomes presented in this systematic review used questionnaires and measurement scales, such as intensity, frequency, and duration of pain crisis, as well as mandibular function, all of which must be considered.

Another important aspect highlighted here, despite the low number of individuals analyzed in both studies, is the fact that it was possible to find evidence for some interventions related to pain reduction and the amount of analgesics used by the patients suffering from this clinical condition.

Conclusions

This review was based on two moderate risk of bias studies. Adequate evidence is not reported in the literature to determine the effectiveness and safety of palliative treatments combined with anti-inflammatory (steroidal and nonsteroidal) drugs versus other treatments or lack of treatment in the reduction of the frequency and intensity of the crises of pain in patients with acute or chronic TMJ DDWOR.

However, according to the evidence found in this study, the following should be considered:

1. Rehabilitation seems to be more effective, when compared to medical treatment, regarding the diminution of the need of prescribing more than one analgesic per week;
2. Arthroplasty seems to be more effective, when compared to medical treatment, regarding the diminution of the need of prescribing more than one analgesic per week;
3. Rehabilitation seems to be more effective, when compared to arthroscopic surgery, regarding the diminution of the need of prescribing more than one analgesic per week;
4. Arthroplasty seems to be more effective, when compared to arthroscopic surgery, regarding the diminution of the need of prescribing more than one analgesic per week.

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