EFFICACY OF PHARMACOLOGICAL AGENTS IN THE TREATMENT OF TEMPOROMANDIBULAR JOINT DISORDER: A SYSTEMATIC REVIEW

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ABSTRACT

The aim of this article is to analyse the effectiveness of pharmacological agents for treatment of Wilke’s disease, anterior disc displacement without reduction, post arthroscopy TMJ pain, and internal disc derangement. Research indicates sodium hyaluronate and non-steroidal anti-inflammatory drugs such as piroxicam have the significant role in pain alleviation while treating TMD. Similarly, the use of local anaesthetic drugs such as bupivacaine and mepivacaine in these studies confirms their success to reduce pain levels in patients. However, the usefulness of morphine was found to be limited and questionable, especially when considering its addictive effects.

Keywords: Pharmacological agent, Temporomandibular joint pain, Temporomandibular joint disease, Sodium hyaluronate, Non-steroidal anti-inflammatory drugs, Bupivacaine, Morphine, Mepivacaine.

INTRODUCTION

Temporomandibular disorder (TMD) includes a variety of conditions associated with pain and dysfunction of the temporomandibular joint (TMJ) and the masticatory muscles [1]. Its aetiology is multi factorial and still poorly understood. A variety of possible etiological factors have been studied such as occlusion, depression, stress and anxiety. A variety of symptoms are also possible and may include clicking or grating within the joint, mechanical restrictions (e. g. , limited jaw opening capacity, deviations in the movement patterns of the mandible), headache, stiffness [2, 3], pain in the face or TMJ area, pain during chewing and wide opening of the mouth, ear aches, dizziness and other complaints such as neck or upper back pain [4]. This multi-factorial disease with multiple symptoms has a wide range of treatment modalities which have been under discussion for several years. The therapeutic methods described in the literature are diverse and range from simple conservative cure to complex surgical methods. Treatment may comprise of physical therapy, postural correction, appliance therapy (occlusal splints), biofeedback, pharmacotherapy, transcutaneous electrical nerve stimulation, acupuncture, psychological therapy (cognitive behavioural therapy) and surgery for joint disorders. But no treatment modality has been singled out to be the most appropriate treatment for TMD so far.

The aim of this article is to analyse the effectiveness of pharmacological agents for treatment of Wilke’s disease, anterior disc displacement without reduction, post-arthroscopy TMJ pain, and internal disc derangement. Drugs have been used to treat diseases ever since the existence of man. It is a convenient form of treatment to use and has many advantages. Some drugs used to treat TMD include dextrose, sodium hyaluronate, botulimum toxin, morphine, mepivacaine, non-steroidal anti-inflammatory drugs, Theraflex-TMJ and bupivacaine.

Three databases, Cochrane, Medline and Embase, were searched electronically (from 1960 through July 2014) for relevant randomised control trials concerning the effects of pharmacotherapeutic agents on TMD. The search conducted for keywords “pharmacological agent”, “pharmacological therapy” “drugs” AND “temporomandibular joint disease” “tmj pain” “tmj disease” revealed 395 articles. This was narrowed down to include only “human clinical trials” which came down to 85 articles. Of these only randomized controlled trials were selected. 12 randomized control trials (RCT) were obtained and these were systematically reviewed by both the authors namely V. S. V. and A. S. F. Of these full texts was retrievable for 6 articles for which a quality assessment was done table 2. The quality of these articles was assessed by V. S. V. and A. S. F. based on the sample size, previous estimate of the sample size, study design, case selection description, valid measurement methods, blinding in the measurements, adequate statistics provided and confounding factors. The quality of treatment results was found to be high in three articles and medium in the other three.

The results of the twelve RCT’s that meet the inclusion criteria were tabulated (table 2). The following parameters were evaluated namely the sampling method, the methodology of the treatment procedure done and the treatment outcome.

Table 1: Articles which met the inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Aim</th>
<th>Type of study</th>
<th>Sample size</th>
<th>Method</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Huddleston</td>
<td>2012</td>
<td>To compare the effectiveness of dexamethasone administration following arthrocentesis of the temporomandibular joint (TMJ) with a placebo (saline)</td>
<td>parallel double-blind RCT</td>
<td>Twenty-eight participants with TMJ arthralgia</td>
<td>arthrocentesis followed by: single-dose intra-articular dexamethasone in one group and saline was administered as a control</td>
<td>Intra-articular dexamethasone following arthrocentesis did not improve the procedure’s effect in patients presenting with TMJ arthralgia</td>
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<tr>
<td>Slater JJ et al</td>
<td>[5]</td>
<td></td>
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<tr>
<td>Refai H et al</td>
<td>2011</td>
<td>To assess the efficacy of dextrose prolotherapy for the treatment of temporomandibular hypermobility</td>
<td>randomised double-blind clin</td>
<td>12 patients with painful subluxation or dislocation</td>
<td>active group-4 injections of dextrose solution (2 mL of 10% dextrose and 1 mL of 2% mepivacaine)</td>
<td>Prolotherapy with 10% dextrose appears promising for the treatment of symptomatic TMJ hypermobility</td>
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</tbody>
</table>

[1] Refai H, Slater J, Huddleston et al. (2011) Temporoman-
<table>
<thead>
<tr>
<th>Year</th>
<th>Study Title</th>
<th>Authors</th>
<th>Study Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Morey-Mas et al [9]</td>
<td>Iverson et al [10]</td>
<td>Pilot study</td>
<td>Forty-one patients with Wilkes stage II disease</td>
<td>Experimental group received 1 mL IA infiltration of saline solution with morphine and placebo.</td>
<td>An intra-articular injection of saline solution during arthroscopy is effective in reducing pain in patients with TMJ dysfunction, enhancing postsurgical recovery.</td>
</tr>
<tr>
<td>2008</td>
<td>Guida-Nardini et al [11]</td>
<td>Zuniga JR et al [12]</td>
<td>Double-blind, placebo-controlled trial</td>
<td>Twenty patients (ten males, ten females; age range 25-45)</td>
<td>Treatment group (ten subjects treated with bovine toxin injections-BTXA) and control group (ten subjects treated with saline placebo injections).</td>
<td>Results from the present study supported the efficacy of BTX-A to reduce myofascial pain symptoms in bruxers, and provided pilot data which need to be confirmed by further research using larger samples.</td>
</tr>
</tbody>
</table>

The table above summarizes the efficacy of botulinum toxin type A (BTX-A) in the management of temporomandibular joint (TMJ) pain, focusing on the use of saline solution and mepivacaine for reducing pain and improving joint function. The study by Ermberg et al. [7] compared the efficacy of saline solution and mepivacaine with placebo on the reduction of postoperative pain, concluding that saline solution is a safe, effective, and quick method of reducing pain. The study by Morey-Mas et al. [9] investigated the use of saline solution during arthroscopy, reporting its effectiveness in reducing pain in patients with TMJ dysfunction. Lastly, Guida-Nardini et al. [11] evaluated the efficacy of saline solution and mepivacaine for reducing pain, concluding that saline solution is an effective method for reducing pain and improving joint function in patients with TMJ pain.
Minakuchi H et al [12] 2004 to identify the appropriate treatment element for initial anterior disc displacement without reduction subjects RCT 69 patients with temporomandibular joint disc displacement without reduction confirmed on magnetic resonance images and was 50 mm or greater on a 100-mm pain scale 3 experimental treatment groups. The treatment of group 1 consisted of short-term nonsteroidal anti-inflammatory drugs and self-care instructions (palliative care group); group 2, nonsteroidal anti-inflammatory drugs, self-care instructions, and occlusal appliance and mobilization therapy (physical medicine group); and group 3, no treatment (control group) palliative care would be more appropriate as the initial therapy to treat painful anterior disc displacement without reduction

Lobo SL et al [13] 2004 to evaluate the effectiveness of the topical cream Theraflex-TMJ (NaBob/Rx, San Mateo, CA) in patients with masseter muscle pain and temporomandibular joint pain (TMJ) randomized, double-blind study Fifty-two subjects apply a cream over the afflicted masseter muscle(s) or over the jaw joint(s) twice daily for two weeks. Theraflex-TMJ cream was used by the experimental group, while a placebo cream was used by the control group

Shi ZD et al [14] 2002 To assess the effect of sodium hyaluronate (HA) for degenerative disorders of the temporomandibular joint (TMJ). RCT 14 cases with synovitis, 21 with anterior disc displacement without reduction and 28 with osteoarthritis of the TMJ. Thirty-five patients allocated in HA group and 28 in PS group

Furst IM et al [15] 2001 Investigation evaluated the efficacy of using intra-articular morphine, bupivacaine, or a combination of both in the management of postarthroscopy temporomandibular joint pain. RCT 4 groups. Group 1 received a sterile saline solution (control), group 2 received bupivacaine alone, group 3 received only a morphine solution, and group 4 received morphine mixed with bupivacaine.

Yuasa H et al [16] 2001 Adequate Yes RCT Adequate 2 groups, consisting of NSAID and physical therapy and a nontreated control group. Both groups were observed at 2 weeks and, for those patients who did not show any improvement, again at 4 weeks. A combination of NSAID and physical therapy for 4 weeks is effective as a primary treatment of patients with disk displacement without reduction and without osseous changes.

Table 2: showing quality evaluation of 6 studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample Size</th>
<th>Previous estimate Size</th>
<th>Study design</th>
<th>Case selection description</th>
<th>Valid measurement Methods</th>
<th>Blinding in measurements</th>
<th>Adequate statistics provided</th>
<th>Confounding factors</th>
<th>Judged quality standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliveras-Moreno J et al [9]</td>
<td>Adequate</td>
<td>Yes</td>
<td>RCT</td>
<td>Adequate</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Medium</td>
</tr>
<tr>
<td>Moneu-Mas MA et al [9]</td>
<td>Adequate</td>
<td>Yes</td>
<td>RCT</td>
<td>Adequate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>Minakuchi H et al [12]</td>
<td>Adequate</td>
<td>Yes</td>
<td>RCT</td>
<td>Adequate</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Medium</td>
</tr>
<tr>
<td>Yuasa H et al [16]</td>
<td>Adequate</td>
<td>Yes</td>
<td>RCT</td>
<td>Adequate</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Furst IM et al [15]</td>
<td>Adequate</td>
<td>Yes</td>
<td>RCT</td>
<td>Adequate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Zuniga JR et al [11]</td>
<td>Adequate</td>
<td>Yes</td>
<td>RCT</td>
<td>Adequate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
</tbody>
</table>
DISCUSSION

Temporomandibular disease is chronic, insidious and is one of the challenging problems in dental practice. Clyde H Wilkes classified TMJ disease based on the symptoms as the disease progressed. There are five stages of disease progression. In stage 2 there is occasionally painful clicking, intermittent locking of the jaw and headaches. The jaw is displaced and slightly forward. This is the beginning of deformity and there is a slight thickening of the posterior edge [17]. Wilkes stage 3 is characterised by frequent pain along with joint tenderness, headaches, pain during mastication, locking of jaw and restricted mouth opening. Anterior disc displacement of the jaw with significant deformity or prolapse of disc also appears. Wilkes stage 4 symptoms are chronic pain with frequent headaches and restricted motion. There is an increase in severity from Stage III with clearly moderate degenerative changes. This is characterized by flattening of the eminence, deformation of the condylar head, and sclerosis. Stage 5 is the last and most severe stage. It is characterised by variable pain, joint crepitus, and painful functioning. Disc perforation, filling defects, gross anatomic deformity of disc and hard tissues accompanied by degenerative arthritic changes are experienced.

Various pharmacological agents have been used to alleviate TMJ pain. Of these denacemethasone, dextrose, botulinum toxin, sodium hyaluronate, methacarbomol/pantetanol, morphine, mepivacaine, bupivacaine have been found to be effective.

Sodium hyaluronate therapy

A study was conducted by Oliveras-Moreno et al [9] to evaluate the efficiency and safety of sodium hyaluronate in the treatment of Wilkes stage 2 disease of the temporomandibular. Forty one patients with Wilke’s stage 2 disease were randomized into 2 groups (study groups-20 and control group-21). The experimental group received sodium hyaluronate therapy and showed a statistically significant (P<0.5) decrease in pain, improvement in mouth opening and decrease in pain at mastication on the end of 56 days [9]. Their TMJ function improved and no adverse reactions to sodium hyaluronate were detected.

Sodium hyaluronate+ringer lactate after arthroscopy

Another study conducted by Morey-Mas et al on the role of sodium hyaluronate after arthroscopic lysis and lavage on forty patients with Wilkes stage 3 and 4 disease randomized into 2 groups. The study group was administered 1 ml sodium hyaluronate+ringer lactate after arthroscopy. Statistically significant decrease (P<0.5) in joint pain was detected in the study group from day 14 and day 94. No statistical difference was observed between the 2 groups in maximum intercusal opening and tolerance [8]. The study results were comparable with those of Oliveras-Moreno et al [9] for the same interval of treatment. But this study does not evaluate pain during mastication. However, both studies reported no adverse reactions to sodium hyaluronate when used for treating patients with TMJ disorders.

Shi ZD et al [14] assessed the effect of sodium hyaluronate on degenerative disorders of the temporomandibular joint (TMJ). 14 cases with synovitis, 21 patients with anterior disc displacement without reduction and 28 with osteoarthritis of the TMJ were selected. Thirty-five patients were allocated in sodium hyaluronate group and 28 in the control group. The study group received injections 6 mg of sodium hyaluronate in the upper compartments of the involved TMJ, whereas the control group received prednisolone 12.5 mg once a week. They concluded that intra-articular injection of sodium hyaluronate is effective and safe to treat TMJ degenerative disorders with mild adverse reactions, better in terms of an effective rate and declined level of IL-6 than prednisolone.

Nonsteroidal anti-inflammatory drugs (NSAID)

NSAID + self-care instructions versus NSAID + self-care instructions + occlusal splints + mobilization therapy

Minakuchi et al conducted a study were sixty nine patients with painful disk displacement without reduction were randomly divided into 3 groups to analyse non-surgical treatment of anterior disc displacement without reduction. Group 1 (palliative group) contained patients treated with short-term NSAID and self-care instructions. Group 2 (physical medicine group) contained patients treated with NSAID, self-care instructions, occlusal splint and mobilization therapy. Group 3 (control group) no treatment was given. Improvement scores of those in group 1 were significantly better than those in group 2 and 3 [12]. At the end of the study short term NSAID and self care instructions had the best values (P<0.04, P<0.01, P<0.05 at 2, 4 and 8 weeks respectively) [12].

NSAID and physical therapy

Yuasa et al study results is similar to the study by Minakuchi et al. Yuasa et al study consisted of sixty patients with painful disk displacement without reduction and without osseous changes randomly divided into 2 groups (study group=30 and control group=30). Study group patients received NSAID and physical therapy. Results showed 60% improvement in the treatment group during 4 weeks of the study [16].

Both studies proved that NSAID and physical therapy administered for 4 weeks to be effective as primary treatment for patients with disc displacement without reduction [16].

Yuasa et al also conducted a study to evaluate the efficacy of ampirocim in TMD (27mg). Ampiroxicam is a pro drug derivative of piroxicam group of NSAIDs. Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) group that can cause serious gastrointestinal bleeding, perforation and ulceration. However, the pro drug is found to have less severe manifestations of side-effects as compared to its therapeutic efficacy [18].

Opioids+local anaesthetics

Bupivacaine versus morphine alone versus morphine mixed with bupivacaine

Furst et al conducted a study on the use of intra-articular opioids and bupivacaine for analgesia following TMJ arthroscopy. Thirty two patients with internal disc derangement and persistent pain who underwent TMJ arthroscopy were randomized into 4 groups (group 1 – control, group 2 – bupivacaine alone, group 3 – morphine alone, group 4 – morphine mixed with bupivacaine). Results showed that bupivacaine alone showed lower pain scores compared to the other groups at 4, 6, and 8 hours post-arthroscopy [15]. Results at the end of 24 hours revealed both groups treated with morphine and bupivacaine alone showed lesser pain scores than the other 2 groups [15].

Mepivacaine versus morphine versus morphine mixed with mepivacaine

A study by Zuniga et al to evaluate the analgesic effect and safety of intra-articular morphine and mepivacaine following TMJ arthroplasty was similar to the study by Furst et al study with the exception that mepivacaine was used instead of bupivacaine. Thirty five patients who underwent TMJ arthroplasty were divided into 4 groups (group c – control, group MEP – mepivacaine alone, group M – morphine alone, group M/MEP – morphine mixed with mepivacaine). Results showed that the mepivacaine and a mixture of morphine and mepivacaine showed better effect compared to the placebo [11]. According to Zuniga et al the local anaesthetic, mepivacaine when given alone was safe, provided quickest, long acting and most effective analgesia [11].

Mepivacaine and bupivacaine are local anaesthetic drugs belonging to the amino amide group. They are relatively safe with their most common side-effect being allergic reactions which are easily preventable by administration of test doses.

Morphine is an opioid analgesic drug. In clinical medicine, morphine is regarded as the gold standard of analgesics used to relieve intense pain. Nevertheless morphine has a high potential for addiction; tolerance and psychological dependence develop rapidly, making its use debatable.

Dexamethasone

Huddleston Slater JJ et al [5] compared the effectiveness of dexamethasone administration following arthrocentesis of
the temporomandibular joint (TMJ) with a placebo (saline). Twenty-eight patients were randomly administered single dose intra-articular dexamethasone in one group and saline in another group following TMJ arthralgia arthrocentesis. Intra-articular dexamethasone following arthrocentesis did not improve the procedure’s effect in patients presenting with TMJ arthralgia.

**Dextrose**

Refai H et al [6] assessed the efficacy of dextrose prolotherapy for the treatment of temporomandibular joint (TMJ) hypermobility. 12 patients with painful subluxation or dislocation of the TMJ were randomly administered four injections of dextrose solution in the study group (2 mL of 10% dextrose and 1 mL of 2% mepivacaine) for each TMJ, each 6 weeks apart whereas the placebo group was injected a placebo solution (2 mL of saline solution and 1 mL of 2% mepivacaine) on the same schedule. Prolotherapy with 10% dextrose appeared to be effective in the treatment of symptomatic TMJ hypermobility.

**Botulinum toxin**

Ernberg M et al [7] studied the efficacy of botulinum toxin type A (BTX-A) in patients with persistent myofascial temporomandibular disorders (TMD). In a randomized, placebo-controlled, crossover multicenter study of twenty one patients with myofascial TMD without adequate pain relief, after conventional treatment a total of 50 units of BTX-A or isotonic saline (control) was randomly injected into 3 standardized sites of the painful masseter muscles. Results did not indicate a clinically relevant effect of BTX-A in patients with persistent myofascial TMD pain. This result was contradicted by Guarda-Nardini L et al [10] who assessed the efficacy of type A botulinum toxin (Botox, Allergan, Inc. Irvine, CA) to treat myofascial pain symptoms and to reduce muscle hyperactivity in bruxers. Ten subjects were randomly assigned to the treatment group treated with botulinum toxin injections-BTX-A and ten patients were treated with saline placebo injections. Results showed that BTX-A was effective in reducing myofascial pain symptoms in bruxers and provided pilot data which need to be confirmed by further research using larger samples.

**Commercial available topical cream for TMD**

Lobo SL, et al [13] evaluated the effectiveness of the topical cream Theraflex-TMJ (NaBob/Rx, San Mateo, CA) in patients with masseter muscle pain and temporomandibular joint (TMJ) pain. Fifty-two subjects applied the cream over the afflicted masseter muscle(s) or over the jaw joint(s) twice daily for two weeks. Theraflex-TMJ cream was used by the experimental group, while a placebo cream was used by the control group. Theraflex-TMJ topical cream is safe and effective in reducing pain in the masseter muscle and the temporomandibular joint.

**CONCLUSION**

Thus, pharmacological agents can be effective in the treatment of Wilke’s disease, anterior disc displacement without reduction, post arthroscopy TMJ pain, and internal disc derangement. It was found that sodium hyaluronate and non-steroidal anti-inflammatory drugs such as piroxicam have a significant role in pain alleviation while treating TMD. Similarly, local anesthetic drugs such as bupivacaine and mepivacaine have been found to be successful in reducing pain levels in patients. However, the usefulness of morphine was found to be limited and questionable, especially when considering its addictive effects.

Dexamethasone was not effective in the treatment of TMJ disease. Dextrose prolotherapy with 10% dextrose was effective in treating symptomatic TMJ hypermobility. Botulinum toxin type A was controversial with one study supporting its effectiveness while the other negating it. Commerciaally available topical creams have also been found to be effective in reducing pain in the masseter muscle and TMJ pain.

**CONFLICT OF INTERESTS**

Declared None

**REFERENCES**