Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 4, 2015

Review Article

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

VIDYA V. S.[1], A. SUMATHI FELICITA[2]

[1]Resident, Saveetha Dental College and A. Sumathi Felicita is the second author. Department of Orthodontics, [2]Saveetha Dental College, India
Email: vsv151291@gmail.com

Received: 27 Sep 2014 Revised and Accepted: 28 Oct 2014

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, botulinum 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 pain" "temporo mandibular 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

Author	Year	Aim	Type of study	Sample size	Method	Conclusion
Huddleston Slater JJ *et al*. [5]	2012	To compare the effectiveness of dexamethasone administration following arthrocentesis of the temporomandibular joint (TMJ) with a placebo (saline).	parallel double-blind RCT.	Twenty-eight participants with TMJ arthralgia	arthrocentesis followed by: single-dose intra-articular dexamethasone in one group and saline was administered as a control	Intra-articular dexamethasone following arthrocentesis did not improve the procedure's effect in patients presenting with TMJ arthralgia
Refai H *et al* [6]	2011	to assess the efficacy of dextrose prolotherapy for the treatment of temporomandibular	randomized, double-blind clin	12 patients with painful subluxation or dislocation of	active group-4 injections of dextrose solution (2 mL of 10% dextrose and 1 mL of 2% mepivacaine) for	Prolotherapy with 10% dextrose appears promising for the treatment of symptomatic TMJ hypermobilit

		joint (TMJ) hypermobility	ical study	the TMJ	each TMJ, each 6 weeks apart, Placebo group-inj. o.f. placebo solution (2 mL of saline solution and 1 mL of 2% mepivacaine) on the same schedule.	y
Ernberg M *et al* [7]	2011	efficacy of botulinum toxin type A (BTX-A) was investigated in patients with persistent myofascial temporomandibular disorders (TMD)	randomized, placebo-controlled, crossover multicenter study	21 patients with myofascial TMD without adequate pain relief after conventional treatment	total of 50 U of BTX-A or isotonic saline (control) was randomly injected into 3 standardized sites of the painful masseter muscles	Results do not indicate a clinical relevant effect of BTX-A in patients with persistent myofascial TMD pain.
Morey-Mas *et al* [8]	2010	use of an intra-articular injection of sodium hyaluronate (SH), when compared with Ringer lactate lavage, result in better postoperative pain control and temporomandibular joint (TMJ) function among patients with Wilkes stage III and IV disease undergoing arthroscopic lysis and lavage	randomized, double-blind, pilot controlled clinical trial	40 patients with late stage wilkes III and early stage IV	treatment group received Ringer lactate plus an injection of 1 mL of SH after arthroscopy control group was given Ringer lactate during arthroscopy	An intra-articular injection of SH after arthroscopic lysis and lavage is effective in reducing pain in patients with TMJ dysfunction, enhancing postsurgical recovery. The analgesic effect of treatment with SH is maintained in the long term.
Oliveras-Moreno JM *et al* [9]	2008	To show whether an intra-articular (IA) infiltration of 1 mL sodium hyaluronate (SH) into the temporomandibular joint (TMJ) would significantly reduce pain and improve joint function in Wilkes stage II disease, compared with the oral administration of a combination of methocarbamol and paracetamol.	RCT	Forty-one patients with Wilkes stage II disease	experimental group received 1 ml IA infiltration of SH with assessments at days 14, 28, 56, and 84 Control group was given 2 tablets of a combination of methocarbamol 380 mg and paracetamol 300 mg every 6 hours for 4 weeks, with assessments at days 14 and 28.	An intra-articular infiltration of SH showed better efficacy in reducing pain and improving joint function in Wilkes stage II disease compared with the oral administration of methocarbamol-paracetamol tablets.
Guarda-Nardini L *et al* [10]	2008	to assess the efficacy of type A botulinum toxin (Botox, Allergan, Inc. Irvine, CA) to treat myofascial pain symptoms and to reduce muscle hyperactivity in bruxers	preliminary double-blind, controlled placebo, randomized clinical trial	Twenty patients (ten males, ten females; age range 25-45) with a clinical diagnosis of bruxism and myofascial pain of the masticatory muscles	Treatment group (ten subjects treated with botulinum toxin injections-BTX-A) and a control group (ten subjects treated with saline placebo injections).	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.
Zuniga JR *et al* [11]	2007	Evaluate the efficacy and safety of intra-articular morphine, mepivacaine, or a combination of both in the management of temporomandibular joint (TMJ) pain in a 24-hour period after arthroplasty.	randomized, double-blind, prospective, parallel, placebo-controlled	35 patients who underwent TMJ arthroplasty.	4 groups: Group M (morphine) received 1 mg of morphine sulfate in 1 mL of saline; group MEP (mepivicaine) received 30 mg of mepivacaine hydrochloride in 1 mL of saline; group M/MEP received 30 mg of mepivacaine hydrochloride and 1 mg of morphine in 1 mL of saline; and group C (saline control) received 1 mL of saline Patients received a single dose of study medication when their postoperative pain reached a moderate or severe intensity	All intra-articular TMJ injections of active substances provided better analgesia than placebo. Morphine alone provided only mild and short-acting analgesia. The local anesthetic, mepivacaine given alone was safe, provided the quickest, longest acting and most effective analgesia. This study suggests that local anesthetics are superior analgesics when given intra-articularly for postoperative TMJ surgery pain and should be investigated for dose response and multiple or continuous infusion effectiveness

					and was 50 mm or greater on a 100-mm pain scale	
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	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	strongly suggest that Theraflex-TMJ topical cream is safe and effective for reducing pain in the masseter muscle and the temporomandibular joint
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	experimental group received injections in the upper compartments of the involved TMJs with 1% HA 6 mg, whereas the control group received prednisolone (PS) 12.5 mg once a week	Intra-articular injection of HA is effective and safe to treat TMJ degenerative disorders with mild adverse reactions, better in terms of effective rate and declined level of IL-6 than PS.
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 temporomandibularjoint (TMJ) pain.	RCT	Thirty-two consecutive patients with internal derangements of the TMJ and persistent pain underwent TMJ arthroscopy.	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.	Bupivacaine alone provides a better analgesic effect than morphine alone or the combination of morphine and bupivacaine. Morphine alone has a longer time of onset, with less effect on the pain scores during the 24-hour observation period
Yuasa H*et al* [16]	2001	effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy for disk displacement without reduction	RCT	Sixty patients with painful disk displacement without reduction and without osseous changes	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

Author	Sample Size	Previous estimate Size	Study design	Case selection description	Valid measurement Methods	Blinding in measurements	Adequate statistics provided	Confounding factors	Judged quality standard
Oliveras-Moreno JM *et al* [9]	Adequate	Yes	RCT	adequate	yes	No	yes	No	Medium
Morey-Mas MA *et al* [8]	Adequate	Yes	RCT	adequate	yes	Yes	yes	No	High
Minakuchi H *et al* [12]	Adequate	Yes	RCT	adequate	yes	No	yes	No	Medium
Yuasa H *et al* [16]	Adequate	Yes	RCT	adequate	yes	No	yes	No	Medium
Furst IM *et al* [15]	Adequate	Yes	RCT	adequate	yes	Yes	yes	No	High
Zuniga JR *et al* [11]	Adequate	Yes	RCT	adequate	yes	Yes	yes	Yes	High

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 dexamethasone, dextrose, botulinum toxin, sodium hyaluronate, methocarbomol/paracetamol, 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 on mastication at 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 hyalronate 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 84. No statistical difference was observed between the 2 groups in maximum interincisal 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=.04, P<.01, P=.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 gropus-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 ampiroxicam 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].

Mepivcaine 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 participants 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 was 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 temporo mandibular 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 hyalronate and non-steroidal anti-inflammatory drugs such as piroxicam have a significant role in pain alleviation while treating TMD. Similarly, local anaesthetic 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. Commercially 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

1. Di Fabio RP. Physical therapy for patient with TMD: a descriptive study of treatment, disability, and health status. J Orofac Pain 1998;12:124–35.
2. Hentschel K, Capobianco DJ, Dodick DW. Facial pain. Neurol 2005;11:244-9.
3. Riley JL, Gilbert GH. Orofacial pain symptoms: an interaction between age and sex. Pain® 2001;90:245-56.
4. Wong Y, Cheng J. A case series of temporomandibular disorders treated with acupuncture, Occlusal splint and point injection therapy. Acupunct Med 2003;21:138-49.
5. Huddleston Slater JJ, Vos LM, Stroy LP, Stegenga B. Randomized trial on the effectiveness of dexamethasone in TMJ arthrocentesis. J Dent Res 2012;91:173-8.
6. Refai H, Altahhan O, Elsharkawy R. The efficacy of dextrose prolotherapy for temporomandibular joint hypermobility: a preliminary prospective, randomized, double-blind, placebo-controlled clinical trial. J Oral Maxillofac Surg 2011;69:2962-70.
7. Ernberg M, Hedenberg-Magnusson B, List T, Svensson P. Efficacy of botulinum toxin type A for treatment of persistent myofascial TMD pain: A randomized, controlled, double-blind multicenter study. Pain ® 2011;152:1988-96.
8. Morey-Mas MA, Caubet-Biayna J, Varela-Sende L, Iriarte-OrtabeJI. Sodiumhyaluronate improves outcomes after arthroscopic lysis and lavage in patients with Wilkes stage III and IVdisease. J Oral Maxillofac Surg 2010;68:1069-74.
9. Oliveras-Moreno JM, Hernandez-Pacheco E, Oliveras-Quintana T, Infante-Cossio P, Gutierrez-Perez JL. Efficacy and safety of sodium hyaluronate in the treatment of Wilkes stage II disease. J Oral Maxillofac Surg 2008;66:2243-6.
10. Guarda-Nardini L, Manfredini D, Salamone M, Salmaso L, Tonello S, Ferronato G. Efficacy of botulinum toxin in treating myofascial pain in bruxers: A controlled placebo pilot study. Cranio ® 2008;26:126-35.
11. Zuniga JR, Ibanez C, Kozacko M. The analgesic efficacy and safety of intra-articular morphine and mepivicaine following temporomandibular joint arthroplasty. J Oral Maxillofac Surg 2007;65:1477-85.
12. Minakuchi H, Kuboki T, Maekawa K, Matsuka Y, Yatani H. Self-reported remission, difficulty, and satisfaction with nonsurgical therapy used to treat anterior disc displacement without reduction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;98:435-40.
13. Lobo SL, Mehta N, Forgione AG, Melis M, Al-Badawi E, Ceneviz C, Zawawi KH. Use of Theraflex-TMJ topical cream for the treatment of temporomandibular joint and muscle pain. Cranio® 2004;22:137-44.
14. Shi ZD, Yang F, Zhang JY, Shi B. Randomized controlled trial of sodium hyaluronate for degenerative disorders of the temporomandibular joint. Chin J Repar Reconstr Surg 2002;16:11-5.
15. Furst IM, Kryshtalskyj B, Weinberg S. The use of intra-articular opioids and bupivacaine for analgesia following temporomandibular joint arthroscopy: A prospective, randomized trial. J Oral Maxillofac Surg 2001;59:979-8316.
16. Yuasa H, Kurita K. Randomized clinical trial of primary treatment for temporomandibular joint disk displacement without reduction and without osseous changes: A combination of NSAIDs and mouth-opening exercise versus no treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:671-5.
17. Clyde H. Wilkes internal derangements of the temporomandibular joint pathological variations. Arch Otolaryngol Head Neck Surg 1989;115:469-77.
18. Longqin Hu. Prodrugs: Effective solutions for solubility, Permeability and Targeting Challenges. I Drugs 2004;7:736-42.