RESEARCH PAPER

TMJ Arthrocentesis Alone and in Combination with Duloxetine in Temporomandibular Joint Pain

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Abstract

Purpose The purpose of the study was to compare the efficacy of arthrocentesis alone and arthrocentesis with duloxetine in patients with TMJ pain.

Materials and methods This study comprised of 20 patients. Patients with TMJ pain as confirmed by RDC/TMD and with pain duration of at least 3 months were included in the study. Patients were randomly divided into two groups, group A in which patients were treated with arthrocentesis alone and group B in which patients were treated with arthrocentesis followed by duloxetine 30 mg twice daily for 12-week therapy. Patients were followed up at regular interval at day 1, day 5, day 7, week 4, week 6 and week 12. Outcome assessment of pain, swelling, maximal mouth opening, painful/pain-free lateral or protrusive jaw movement was done. Hospital anxiety and depression (HAD) scale was used to assess pre- and post-treatment anxiety and depression. Radiologic assessment was done based on OPG and CBCT. Biochemical assessment of IL-6 in lavage fluid between groups A and B was done pre-operatively and postoperatively.

Results There was significant reduction of pain in both groups, but reduction of pain was more in group B than in group A at week 4, week 6 and week 12. Mouth opening was significantly higher in group B than in group A patients. Reduced painful lateral and protrusive movements were seen in group B than in group A patients. There was no significant difference in hospital anxiety and depression

scale among the groups at pre-operative and at 4th week post-operative. Though a significant reduction of IL-6 levels was seen post-operatively, there was no significant difference between the two groups.

Conclusion Arthrocentesis is an effective procedure for relieving symptoms in patients with temporomandibular disorders. In this study, combination of duloxetine with arthrocentesis gave much better outcome than arthrocentesis alone. Further studies with large sample size required to evaluate the effect of arthrocentesis plain or in combination with duloxetine in providing permanent relief to the patient.

Keywords Duloxetine · TMJ Pain · TMJ Arthrocentesis

Introduction

Temporomandibular joint disorder was first defined by Hey et al. as a localized mechanical faults interfering with the smooth functioning of a joint. Temporomandibular joint pain is one of the distress symptoms, and it disturbs the daily life. The majority of patients with disc displacements have no symptoms, but some patients with disc displacements may experience pain and reduced mouth opening when the disc does not reduce to a normal position on opening. Pain and jaw limitation often have an impact on daily life function, psychosocial well being and quality of life in TMD patients. Several interventions have been suggested for the treatment of disc displacements without reduction (DDwoR). Lavage of the TMJ with or without steroid injections has been reported to be effective in reducing pain and in to improve jaw mobility patients with disc displacement without reduction (DDwoR) [1]. The analgesic efficacy of duloxetine has been demonstrated in

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four distinct chronic pain conditions. These include diabetic peripheral neuropathy, fibromyalgia, chronic low back pain, and osteoarthritis knee pain. Duloxetine a potent selective serotonin and nor epinephrine reuptake inhibitor may correct a functional deficit of serotonin and norepinephrine neurotransmission. It is hypothesized that potentiation of 5-HT and NE activity in the CNS results in pain inhibition [2]. Duloxetine has also been evaluated in three separate double-blind, randomized, placebo-controlled trials in chronic osteoarthritis knee pain (OAKP). The recommended dose for OAKP is 60 mg once daily. A lower starting dose of 30 mg may be considered for tolerability reasons in some patients, with a target dose of 60 mg/day within 1–2 weeks [3]. A concerted effort is underway to ensure that clinical trial research in pain is conducted according to the best available standards. The initiative on methods, measurement, and pain assessment in clinical trials (IMMPACT) aims to systematically address the challenges related to pain research and has proposed recommendations related to clinical trial methodology and design [5].

Manfredini et al. [4] concluded from their study that patients with myofascial pain have a different prevalence of psychiatric symptoms to patients with no TMD, those with disc displacement, and those with joint disorders. In fact, myofascial pain patients showed the highest prevalence of both mood and anxiety psychopathology when compared with TMD-free, disc displacement, and joint disorders subjects. In particular, myofascial pain subjects presented significantly higher scores for a number of depression-related domains of MOODS-SR and for PAS-SR domains investigating panic, stress sensitivity, separation anxiety, and agoraphobic symptoms. Effect of duloxetine on pain intensity in the majority of RCTs evaluating analgesic efficacy utilise reduction in pain intensity as their primary outcome measure. Visual analog scales, numerical rating scales, and verbal rating scales have all been demonstrated as being valid and reliable measures of pain [5]. Chappell et al. [6] and OA-2 Chappell et al. [7] revealed that duloxetine patients were 33% more likely to have a clinically meaningful response to treatment than placebo patients and that the number needed to treat (NNT) = 6. In addition, increasing the dose of duloxetine to 120 mg/day did not confer any additional benefit in either age category.

Pathway of TMJ Pain

Pain signals are also modulated via descending pathways [2]. These pathways travel down from the brain to subcortical nuclei within the mid-brain until they reach the dorsal horn of the spinal cord and can either amplify or

attenuate pain signals. Two essential neurotransmitters involved in the attenuation of pain signals are serotonin (5-HT) and norepinephrine (NE). While 5-HT can both amplify and attenuate pain signals, NE only has an attenuation effect. In addition to 5-HT and NE, opioids and GABA are involved in the inhibition of pain signals, whereas glutamate and aspartate are involved in their amplification [2]. Chronic pain, similar to pain associated with knee OA, results in changes in the CNS, which likely reflect alterations in supraspinal modulation of nociception and include increases in excitatory and decreases in inhibitory modulation pathways [8, Staud 9].

Review

About 60–70% of the general population has at least one sign of a temporomandibular disorder, yet only around one in four people with sign is actually reported. Only about 5% of the people with one or more signs of a temporomandibular disorder (TMJ) will actually seek treatment. TM joint arthrocentesis represents a form of minimally invasive surgical treatment in patients suffering from TM joint disorder. It consists of washing of the joint with normal saline solution with the aim to remove chemical inflammatory mediators and changes in intraarticular pressure. The success rate was reported 83.5%. Dimitroulis et al. [10] also suggest that arthrocentesis should be considered as an alternative to more invasive TMJ surgical procedures.

Methods

Twenty patients were included in the study. The ethical committee approval had obtained before enrolling patients. Detailed examination of dentition and occlusion was carried out to rule out any dental etiology. An informed consent was obtained from patients after explaining the study in detail and their questions answered.

Entry Criteria

- (a) Age—above 18 years.
- (b) Pain on chewing or maximal mouth opening and score—at least 3 on a 0–10 numeric rating scale where the endpoints were 0 = no pain and 10 = worst pain.
- (c) Pain duration of at least 3 months.
- (d) TM joint pain of nonodontogenic origin as confirmed by the research diagnostic criteria for temporomandibular disorders TMD/RDC axis II.
- (e) Females who are neither pregnant nor breast feeding.

Exclusion Criteria

- (a) Pain from traumatic injury. Diagnosed as systemic muscular or joint disease (fibromyalgia, rheumatoid arthritis).
- (b) Disturbed coagulation ability.
- (c) Severe allergic reaction to multiple medications.
- (d) Initiation of or change in unconventional or alternate therapies.

The hospital anxiety and depression scale (HAD scale) [11] was used to access pre- and post-treatment anxiety and depression.

The clinical assessment comprised a temporomandibular joint examination. Routinely panoramic radiographic examination of the all patients was carried out to rule out dental cause of pain and CBCT of the joint. Patients who met entry criteria following screening were treatment groups.

Group A—TMJ arthrocentesis only.

Group B—arthrocentesis followed by duloxetine 30 mg twice daily for 12-week therapy.

Thereafter, study visit was scheduled at 2-week interval. Patients then entered a 1-week drug-tapering phase at which time dosages of study drug were reduced. Patients who reported increased pain and a desire to receive additional treatment at follow-up were withdrawn from the study. During duloxetine therapy, if any adverse effect and deranged liver function test were observed, then patients follow-up will be extended till symptoms disappear. Primary outcome measure as pain severity was measured by self-reported brief pain inventory. The graded chronic pain scale (GCPS) [12] is a self-report instrument that uses seven questions concerning pain intensity, interference in daily activities, and disability days to yield a 0–IV score: grade 0 is defined as no TMD pain, grade I as TMD pain of low intensity, grade II as high intensity pain, and grades III and IV reflect moderate to significant pain-related psychosocial disability. Global improvement with treatment was assessed on a 0–6-point scale (completely well, much better, somewhat better, unchanged, somewhat worse, and much worse). The safety of duloxetine has been assessed by treatment-emergent adverse events, discontinuation pattern, and vital sign.

Arthrocentesis

Arthrocentesis has been described as a simple and effective treatment for patients with internal derangement of the TMJ. Murakami et al. studied the comparison of consecutive patients with disc displacement without reduction and found no significant differences between arthrocentesis,

arthroscopic surgery, and nonsurgical treatment. Efficacy of arthrocentesis in various studies is as follows: Murakami et al.—70%, Dimitroulis et al.—98%, Hosaka et al.—79%, and Nitzen—95%.

Duloxetine

Duloxetine hydrochloride is an antidepressant that inhibits both serotonin and norepinephrine reuptake. The dual acting mechanism of duloxetine makes it particularly interesting in the treatment of depression with cognitive impairment, as imbalance or deficiency in either 5-HT or NE system has been found to contribute cognitive deficiency. Duloxetine is approved for the treatment of fibromyalgia, diabetic neuropathic pain, major depressive disorder, generalized anxiety disorder, and chronic musculoskeletal disorder. The maximal plasma concentration 47 ng/ml is achieved 6 h after dose. The pharmacokinetics of duloxetine exhibits linearity, and the steady state concentration is reached in approximately 3–5 days. Duloxetine has usual life 8–17 h, and about 70% is excreted in urine as metabolites and about 20% of duloxetine excreted in faeces. Duloxetine can cause a multitude of symptoms including headache, dizziness, nightmares, irritability, paresthesia, and nausea/vomiting. Thus, it is recommended that this agent be decreased in small decremental amounts over an extended period of time. Adverse effects that may occur commonly (>10%) include somnolence, dizziness, headache, insomnia, hypertrichosis, sexual dysfunction, diminished appetite, and urinary hesitancy. Other side effects include agitation, erectile dysfunction, nervousness, psychomotor agitation, decreased libido, and restlessness.

Results

The pain was observed to be similar ($p > 0.05$) in both of the groups at pre-op, day 1, day 5, and day 7. The pain was significantly ($p < 0.05$) lower in group B than in group A at week 4, week 6, and week 12 (Fig. 1). Figure 2 shows the comparison of maximum mouth opening across the time period among the groups. The mouth opening was observed to be similar ($p > 0.05$) in both the groups at pre-operatively. The mouth opening was significantly ($p < 0.05$) higher in group B than in group A at day 1 and subsequent follow-ups.

There was no significant ($p > 0.05$) difference in IL-6 in lavage fluid between group A and group B at all the time intervals. A significant decrease was observed in IL-6 in lavage fluid from pre to post in group A ($p = 0.0001$) and group B ($p = 0.001$). None of the group B patients reported any adverse effect during treatment.

Fig. 1 Comparison of pain across the time period among the groups

Fig. 2 Comparison of maximal mouth opening across the time period among the groups

Discussion

All patients subjectively had moderate to severe pain pre-operatively. There was reduction in pain in both the groups, but pain was significantly reduced in group B than in group A at week 4, week 6, and week 12. Pain in group B was much reduced than in group A. Nitzan et al. [13] in their study found almost the same results. These findings are in correlation with the findings of Dimitroulis et al. [14]. According to de Souza et al. [15], TMJ pain improves over time after arthrocentesis. Carvajal and Laskin [16] reported that arthrocentesis can reduce pain and dysfunction in patients with anterior disk displacement both long term and short term. Kunjur et al. [17] reported a significant reduction in pain score following arthrocentesis. Our study findings also correlate with the findings of Emshoff et al. [18], Sanroman [19], Yura and Totsuka [20], and Kaneyama et al. [21].

There was no significant difference in the swelling between both groups at all the follow-up visits. After 1 week, there was statistically significant increase in mouth opening in groups A and B. There was statistically significant difference within the groups. Mouth opening gradually increases over the time during follow-ups. Nitzan et al. [13] in their study found almost same results. These

findings are in correlation with the findings of Dimitroulis et al. [14]. Nitzan et al. [22] reported that arthrocentesis is a valuable tool for improving significant mouth opening. Emshoff et al. [18], Sanroman [19], Yura and Totsuka [20], and Kaneyama et al. [21] in their study found almost the same results. Our study concluded that duloxetine has no beneficial effect on mouth opening parameter.

In this study, there was significant difference in lateral and protrusive movement (painful or painless) among the groups at week 4, week 6, and week 12. Group B had reduced painful lateral and protrusive movements in comparison with group A. These results are similar to published studies by Dimitroulis et al. [10], Stein [23], Nitzan et al. [22], and Carvajal and Laskin [16].

In terms of clinically detectable clicking sound, there was no significant difference in clicking among the groups at all the time intervals. Clicking was reduced in patients of group A as compared to group B. Our finding is in correlation with that of Carvajal and Laskin [16] who found an increase in joint sound post-arthrocentesis in patient having disc displacement with reduction and joint sound not affected in patient having disc displacement without reduction. Our study concluded that clicking was independent of either form of treatment.

There was no significant difference in hospital anxiety and depression rating scale among the groups at pre-op and at 4th week. It means that although there was no difference in the levels of anxiety and depression between the groups, addition of duloxetine was still beneficial over arthrocentesis alone in terms of pain (overall) and pain during lateral and protrusive movements. Mouth opening was a function of arthrocentesis and was not affected by duloxetine.

We estimated IL-6 level in lavage fluid of TMJ disorder patients treated with arthrocentesis (group A) and arthrocentesis along with duloxetine (group B). In our study, mean IL-6 level in lavage fluid of groups A and B patients before intervention, i.e., preoperatively, was 12.69 ± 7.53 and 9.33 ± 5.49 pg/ml, respectively. After 12 weeks of treatment, mean IL-6 values in groups A and B were 5.84 ± 1.53 and 5.05 ± 1.18 pg/ml, respectively. There was a significant decrease in IL-6 levels in both the groups (p value 0.0001 and 0.001). Though there was no significant difference in IL-6 levels in lavage fluid between groups A and B. Studies are available according to which IL-6 in TMJ fluid was associated with acute synovitis, TMJ pain, and inflammation. Takahashi et al. [24] reported in their study that excessive production of cytokines including IL-6 in synovial fluid may contribute to synovitis and were correlated with TMJ arthralgia. In our study also, IL-6 levels were elevated before any intervention in all the patients with TMJ disorders. The levels of IL-6 in fluid were found to be decreased after treatment in groups A and B. Lee et al. [25] in their study found elevated levels of IL-

6 in patients with TMD as compared to healthy controls. Gulen et al. [26] reported the difference between cytokines IL-1 β , IL-6, IL-8, IL-11 and TNF- α levels before and after arthrocentesis. The concentration of cytokines decreased after arthrocentesis which was statistically significant. In our study also, we found a significant decrease in IL-6 levels after 12 weeks of arthrocentesis only (group A). Similarly, levels were also found to be significantly decreased in group B patient treated with arthrocentesis and tablet duloxetine (30 mg BD) for 12 weeks. These declines in IL-6 level in fluid suggest the effectiveness of the treatment in both the groups. As IL-6 plays an important role in pathogenesis of TMJ disorders, analysis of IL-6 in synovial fluid may play an important role in management of these patients. A significant decrease in IL-6 concentration after treatment can serve as a prognostic marker. If the level of IL-6 remains elevated in synovial fluid after treatment, it may serve as an indicator of the failure of treatment.

TMJ arthrocentesis has been used as a treatment modality in TMJ disorders since many years and is known to relieve three common symptoms: limitation in mouth opening, pain, and dysfunction. Though the mechanism of action of arthrocentesis is still not clear, it is believed that inflammatory mediators are washed away in the lavage, resulting in pain reduction. In our study also, we observed that after 12 weeks of treatment there was a reduction in pain and improvement in mouth opening. In our study, group A patients were treated with arthrocentesis in which a significant decrease in IL-6 concentration proved that the arthrocentesis was efficient in removing IL-6 and relieving symptoms in TMJ disorders. Hence, arthrocentesis may be considered as an alternative procedure to invasive surgery in the selected group of patients with TMJ disorders.

In group B, patients were treated with arthrocentesis along with tablet duloxetine for 12 weeks and level of IL-6 was found to be significantly decreased. Duloxetine as an antidepressant has been shown effective in chronic pain in fibromyalgia, diabetic neuropathy, and anxiety and depression.

In our study, the concentration of IL-6 in lavage fluid decreased significantly in both the groups (A and B) after 12 weeks of treatment. On addition of duloxetine, pain was significantly reduced in patients of group B after 12 weeks of treatment as compared to group A without duloxetine. A study by Zhao et al. [27] shows a significant decrease in levels of serum IL-6, TNF- α , and IL-1 after treatment with duloxetine. This may be due to the inhibition of serotonin and norepinephrine reuptake by duloxetine, thereby decreasing production of IL-6 and hence reducing inflammation and pain. As the sample size in our study was small, findings should be considered as preliminary only. Further studies on large sample size are required in future to find

out the effect of duloxetine on IL-6 levels as well as on other cytokines IL-1, IL-8, IL-18, and TNF- α in TMJ disorder. These findings may be attributable to the fact that in patients having disc displacement with reduction in whom adhesion and mechanical locking are not a significant factor, it can be postulated that post-arthrocentesis duloxetine therapy relieves the fibromyalgia and myofascial pain and perhaps reduces anxiety and depression also, so making the post-arthrocentesis phase less painful, and helps in early relief of pain in these kind of patients.

These findings can be explained according to the fact that arthrocentesis abolishes negative pressure and loosens the adhered disc, reinstitutes its free sliding movement in upper joint space, as well as it is also instrumental in removing inflammatory constituents and pain mediators from the joint [28] furthermore, it is proven that although arthrocentesis provides a solution for the symptoms (pain, reduced mouth opening, dysfunction), it does not necessarily have an effect on the underlying causes of these disorders.

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