Original Article

Effect of duloxetine in temporomandibular joint disorders: A comparison with arthrocentesis

ABSTRACT

Purpose: This study was conducted to compare the efficacy of temporomandibular joint (TMJ) arthrocentesis, duloxetine therapy alone, and duloxetine in combination with TMJ arthrocentesis in the treatment of painful TMJ.

Materials and Methods: Thirty patients with TMJ pain were included in the study who were divided into three groups with ten patients in each group. Group A included patients having only TMJ arthrocentesis; in Group B, only duloxetine therapy (30 mg) was given twice a day orally for 3 months; and in Group C, a combination of TMJ arthrocentesis with duloxetine therapy (30 mg) was given twice a day orally for 3 months. Patients were followed at regular interval of the 1st day, 5th day, 7th day, 4th week, 6th week, and 12th week and assessed in terms of pain, maximum mouth opening (mm), clicking, Hospital Anxiety and Depression Rating Scale and estimation of interleukin-6 (IL-6). The data collected were compiled and statistically analyzed.

Results: The pain was found to be significantly lower in Group C than other groups at weeks 4, 6, and 12. In Group C, mouth opening increased significantly than Groups A and B on subsequent follow-ups. On biochemical analysis of IL-6 levels in lavage fluid, a significant decrease was observed in levels of IL-6 in lavage fluid in Groups A and C postoperatively.

Conclusion: The present study states that pain was observed to be much less after arthrocentesis along with duloxetine therapy. This combination therapy leads to much better and faster outcome, but still, long-term follow-ups with larger number of patients are required.

Keywords: Duloxetine, temporomandibular joint arthrocentesis, temporomandibular joint pain

INTRODUCTION

Temporomandibular disorder (TMD) is a musculoskeletal disorder within the masticatory system. It has an adverse effect on jaw function so that patients may present with limited mouth opening or difficult chewing because of pain and locking in the temporomandibular joint (TMJ).[1]

Most TMJ disorders include internal derangement which has been described as conditions in which the articular disc has become displaced from its original position in relation to the condylar head and articular eminence.

The displacement of the disc can result in numerous presentations, with the most common being disc displacement with reduction (with or without intermittent locking) and disc displacement without reduction (with or without limited opening).[2] The disorder has been associated with characteristic clinical findings such as pain, joint sounds, and irregular or deviating jaw function.[3-5] TMJ pain is one of the distress symptoms which disturb the daily life of the patients. The diagnosis should be made on the history, clinical

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examination, investigations (routine as well as specific), and radiographic evaluation.

The management of TMJ-related conditions is necessary because pain limits range of motion, and range of motion is needed to maintain fluid flow in the joint for lubrication between the articular surfaces.

Arthrocentesis is recognized increasingly as the first-line surgical intervention in patients who do not respond to conservative management. The physical action of lysis and lavage in the superior joint space rather than repositioning the disc is thought to be responsible for the success of this procedure.[6-9] Arthrocentesis is thought to break down adhesions within the joint and remove inflammatory mediators including cytokines and interleukins (ILs), which result in chronic pain. Relief of TMJ pain also leads to improvement in both mouth opening and dysfunction.

Centrally active agents such as duloxetine have also been widely studied or used in the treatment of pain associated with osteoarthritis of various joints. Duloxetine is a selective, relatively balanced serotonin (5-hydroxytryptamine) and norepinephrine (NE) reuptake inhibitor. Imbalance of 5-HT and NE has been implicated in chronic pain associated with central sensitization.

In this study, our objective is to investigate the effect of duloxetine in TMJ disorders. We hypothesize that the neurotransmitters released in response to pain in TMJ disorder induce production of various cytokines such as IL-6 promoting inflammation and further aggravating pain. Duloxetine, which acts by inhibiting reuptake of serotonin and NE, may decrease the production of IL-6 reducing inflammation and thus relieving pain in such patients.

Aims and objective

The present study was conducted to compare the efficacy of TMJ arthrocentesis, duloxetine therapy alone, and duloxetine in combination with TMJ arthrocentesis in the treatment of painful TMJ.

MATERIALS AND METHODS

The present study comprised thirty patients with internal derangement visiting the Outpatient Department of Oral and Maxillofacial Surgery, King George's Medical University, Lucknow. Diagnosis was made on the basis of history, clinical examination, and investigations. The treatment plan was thoroughly explained to each patient, and informed consent was taken. The ethical committee approval was obtained.

Inclusion criteria

1. Patients within the age limit between 18 and 60 years of age
2. TMJ pain of non-odontogenic origin as confirmed by the Research Diagnostic Criteria (RDC) for TMD/RDC axis II.
3. Pain on chewing or maximal mouth opening with a duration of at least 3 months.

Exclusion criteria

1. Patients having systemic autoimmune diseases or debilitated diseases
2. Patients having disturbed coagulation ability
3. Severe allergic reaction to multiple medications
4. Pain from traumatic injury.

The clinical assessment comprised TMJ examination. Routinely panoramic radiographic examination and cone-beam computed tomography of the joint were carried out for the all patients to rule out the dental cause of pain as well as to exclude TMJ abnormalities. The Hospital Anxiety and Depression Rating Scale (HAD scale)[10] was used to access pre- and posttreatment anxiety and depression.

Patients who met inclusion criteria following screening were divided into three groups, and each group consists of ten patients.

- Group A: TMJ arthrocentesis with Ringer's lactate (approximately 200 ml) solution
- Group B: Only duloxetine therapy (30 mg) given twice a day orally for 3 months
- Group C: Combination of TMJ arthrocentesis with duloxetine therapy (30 mg) given twice a day orally for 3 months.

Patients were followed at regular interval of the 1st day, 5th day, 7th day, 4th week, 6th week, and 12th week and assessed in terms of the following criteria:

1. Pain: Visual Analog Scale (0–10)
2. Maximum mouth opening (mm): Maximum interincisal distance
3. Clicking: Present/absent
4. HAD scale[10]
5. Estimation of IL-6 was estimated in lavage fluid only in Group A and Group C by arthrocentesis on the first visit and postoperatively at 3 months. In Group B, only duloxetine therapy was given orally.

The diaclone IL-6 enzyme-linked immunosorbent assay kit was used for the quantitative determination of IL-6.

The data were collected, compiled, and then analyzed using the Chi-square test, which compared the categorical variables among the groups. The one-way analysis of variance was used to compare normal discrete variables, and the Kruskal–Wallis test

was used to compare nonnormal discrete variables. $P < 0.05$ was considered statistically significant. All the analysis was carried out on the SPSS 16.0 version by IBM (Chicago, IL, Inc., USA).

RESULTS

The results of the study are summarized as follows:

1. The pain was observed to be similar ($P > 0.05$) in all the groups preoperatively, day 1, day 5, and day 7, but the pain was found to be significantly ($P < 0.05$) lower in Group C than Group A and Group B at week 4, week 6, and week 12 [Figure 1 and Table 1]
2. Preoperatively, the mouth opening was observed to be similar ($P > 0.05$) in all the groups. The mouth opening was observed to be significantly ($P < 0.05$) higher in Group C than Group A and Group B at day 1 and on subsequent follow-ups [Figure 2 and Table 2]
3. There was no significant ($P > 0.05$) difference in clicking among the groups at all the time intervals both preoperatively and postoperatively
4. There was no significant ($P > 0.05$) difference in the HAD scale among the groups at all the time intervals both preoperatively and postoperatively
5. There was no significant ($P > 0.05$) difference in levels of IL-6 in lavage fluid between Group A and Group C by arthrocentesis on the first visit. However, a significant decrease was observed in levels of IL-6 in lavage fluid in Group A ($P = 0.0001$) and Group C ($P = 0.001$) postoperatively [Figure 3 and Table 3].

DISCUSSION

The aim of the study was to compare the efficacy of duloxetine therapy alone or in combination with TMJ arthrocentesis in the treatment of painful TMJ.

All patients taken in Groups A, B, and C had moderate-to-severe pain preoperatively. However, the reduction in pain was observed in all the groups postoperatively. Pain was found to be significantly reduced in Group C in comparison with Group A and Group B at week 4, week 6, and week 12. Pain in Group A was much reduced than Group B but not as much as in Group C [Figure 1 and Table 1]. Dolwick and Nitzan,[11] in their study, found almost the same results. This finding is in correlation with the findings of Dimitroulis *et al*.[12] Kunjur *et al*.[13] also reported a significant reduction in pain score following arthrocentesis. Our study findings also correlate with the findings of Emshoff *et al*.,[14] Sanromán,[9] Yura and Totsuka *et al*.,[15] and Kaneyama *et al*.[16] (2007).

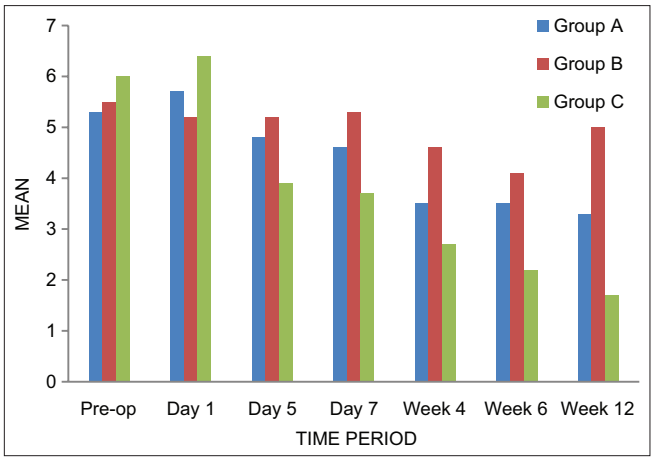

Figure 1: Comparison of pain across the time period among the groups

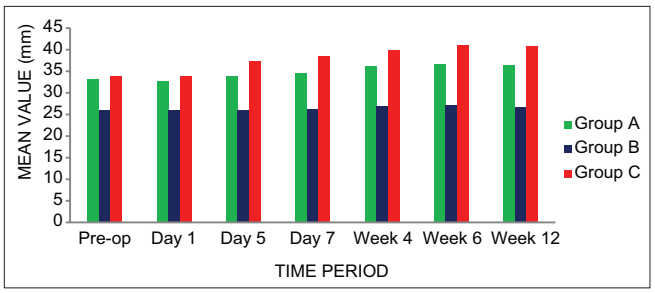

Figure 2: Comparison of maximum mouth opening across the time period among the groups

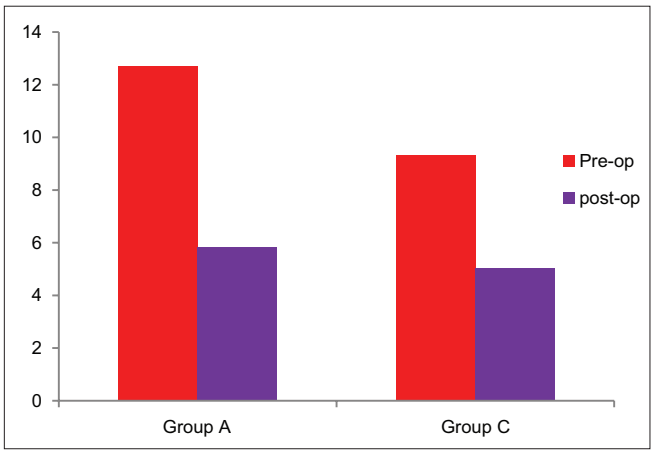

Figure 3: Comparison of lavage fluid

The mouth opening was observed to be similar in all the groups preoperatively but was observed to be significantly higher in Group C than Group A and Group B on subsequent follow-ups [Figure 2 and Table 2]. Dolwick and Nitzan,[11] in their study, found almost the same results. This finding is in correlation with the findings of Dimitroulis *et al*.,[12] Emshoff *et al*.,[14] Sanromán,[9] Yura and Totsuka *et al*.,[15] and Kaneyama *et al*.[16] (2007) in their studies that found almost the same results.

Table 1: Comparison of pain across the time period among the groups

Time period	Mean±SD			*P*[a]
	Group A	Group B	Group C	
Preoperative	5.30±1.25	5.50±1.08	6.00±1.33	0.43
Day 1	5.70±1.56	5.20±1.31	6.40±1.64	0.22
Day 5	4.80±1.61	5.20±1.31	3.90±1.79	0.19
Day 7	4.60±1.61	5.30±1.25	3.70±1.88	0.10
Week 4	3.50±2.01	4.60±1.35	2.70±1.25	0.03*
Week 6	3.50±2.06	4.10±1.59	2.20±1.13	0.04*
Week 12	3.30±2.26	5.00±2.00	1.70±0.67	0.001*

[a]ANOVA test, *Significant. ANOVA: Analysis of variance, SD: Standard deviation

Table 2: Comparison of maximum mouth opening across the time period among the groups

Time period	Mean±SD			*P*[a]
	Group A	Group B	Group C	
Preoperative	33.30±5.67	26.10±4.43	33.90±9.17	0.06
Day 1	32.70±6.89	26.10±4.43	34.00±8.57	0.03*
Day 5	34.00±7.19	26.10±4.43	37.30±9.82	0.007*
Day 7	34.60±7.01	26.20±4.15	38.50±9.84	0.003*
Week 4	36.30±6.58	26.90±4.35	40.00±8.62	0.001*
Week 6	36.70±6.39	27.20±4.31	41.10±7.63	0.001*
Week 12	36.50±6.65	26.70±3.88	40.90±7.59	0.001*

[a]ANOVA test, *Significant. ANOVA: Analysis of variance, SD: Standard deviation

Table 3: Comparison of lavage fluid

	Group A	Group B	Group C	*P*[a]
Preoperative	12.69±7.53	-	9.33±5.49	0.45
Postoperative	5.84±1.53	-	5.05±1.18	0.40

[a]Unpaired *t*-test

There was no significant difference in clicking postoperatively. Clicking was reduced in patients of Group A as compared to Groups B and C, which is in correlation with that of Carvajal and Laskin.[17] Thus, it was found that clicking was independent of either form of treatment or combination of them. There was no significant difference in the HAD scale among the groups at preoperatively and at the 4th week.

In Group A and Group C, the mean IL-6 levels measured in the lavage fluid were 12.69 ± 7.53 pg/ml and 9.33 ± 5.49 pg/ml at the first visit. After 3 months of treatment, the mean IL-6 values in Groups A and C were 5.84 ± 1.53 pg/ml and 5.05 ± 1.18 pg/ml, respectively. On postoperative evaluation, there was a significant decrease in IL-6 levels in both the groups ($P = 0.0001$ and 0.001). However, postoperatively, there is no significant difference between Groups A and C in IL-6 levels in lavage fluid [Figure 3 and Table 3]. Various studies suggested that IL-6 plays an important role in enhancement of T-lymphocyte proliferation, B-lymphocyte differentiation, and complement cascade activation[18] and were also found to be associated with acute synovitis, TMJ pain, and inflammation in TMJ fluid.[19-21] Lee JK *et al*.[22] in their study found that in TMDs, the synovial levels of tumor necrosis factor (TNF)- and IL-6 were elevated in patients having symptoms of acute pain, mouth opening limitation, and clicking. This is in accordance with our study where IL-6 levels were elevated in all the patients with TMJ disorders before any form of treatment was given. However, these levels were found to be decreased after treatment only in Group A and Group C.

The results of the present study are also in agreement with the study conducted by Nishimura *et al*.[23] and Gulen *et al*.[24] who reported that there was a significant difference between cytokines IL-1, IL-6, IL-8, IL-11, and TNF-α levels in patients after arthrocentesis suggesting the effectiveness of the treatment procedure.

Thus, the IL-6 concentration in synovial fluid can serve as a prognostic marker and may assist in the management of patients with TMJ disorders.

Arthrocentesis is a simple safe and minimally invasive technique for the treatment of TMJ disorders. Significant improvements have been reported in terms of reduction in TMJ pain, mouth opening, and clicking or popping sounds in the TMJ following arthrocentesis.[25] During arthrocentesis, it is believed that inflammatory mediators are washed away in the lavage resulting in pain reduction.[8,26]

The results of our study showed that in Group A patients, there was a significant decrease in IL-6 concentration along with a reduction in pain and improvement in mouth opening after 3 months of treatment. Thus, arthrocentesis may be considered as an alternative procedure to invasive surgery in patients with TMJ disorders.

In the present study, it was also observed that the concentration of IL-6 in lavage fluid decreased significantly in both the groups (A and C) after 12 weeks of treatment. The addition of duloxetine caused a significant reduction in pain in patients of Group C. These results are in concordance with the study conducted by Zhao *et al*.[27] which concluded that after treatment with duloxetine, there was a significant decrease in levels of serum IL-6, TNF-α , and IL-1. This may be attributed to the inhibitory effect of duloxetine on serotonin and NE reuptake causing decreased production of IL-6 and thereby reducing inflammation and pain.

In Group C patients, when both arthrocentesis and duloxetine were used together, there was a significant reduction in levels of IL-6. This suggests that postarthrocentesis, duloxetine therapy relieves fibromyalgia and Myofascial pain and perhaps reduces anxiety and depression making the postarthrocentesis phase less painful.

In Group B patients, duloxetine therapy was given alone without arthrocentesis. Since there was no lavage fluid collected, the measurement of IL-6 levels was not possible, and no data were available for comparisons with Groups A and B. Further studies on large sample size are required to find the effect of duloxetine on IL-6 levels as well as help in understanding the complex interaction of duloxetine, inflammation, and cytokines in TMJ disorder.

Therefore, the present study states that arthrocentesis causes relief of TMJ pain and also leads to improvement in both mouth opening and dysfunction. It causes lysis and lavage in the superior joint space rather than repositioning the disc.[5-8] and is also thought to break down adhesions within the joint and remove inflammatory mediators including cytokines and ILs, which result in chronic pain.

CONCLUSION

Arthrocentesis is recognized increasingly as the first-line surgical intervention for relieving symptoms (pain and mouth opening) in patients who do not respond to conservative management with TMDs. In our study, pain was much lesser after arthrocentesis along with duloxetine therapy than arthrocentesis or duloxetine therapy alone. This combination therapy also leads to much better and faster improvement in mouth opening, but still, long-term follow-ups with larger number of patients are required.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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