The Effect of Combination Therapy with Fluoxetine and Clonazepam in Myofacial Pain Dysfunction Syndrome.

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Abstract: Myofacial pain dysfunction syndrome (MPDS) is one of the most common causes of pain in facial region. Psychological problems, especially depression and anxiety are of the most important etiologic factors. The aim of this study was to investigate the effect of combination therapy with fluoxetine and clonazepam in the treatment of MPDS. Fluoxetine and clonazepam were prescribed at the baseline for all patients. Changes in pain severity and tenderness in masticatory muscles, and maximal painless mandibular opening were measured before and after treatment. 90 percent were cured completely, 4 remaining patients were referred to psychiatrist. By considering the efficacy of this treatment modality, we suggest it for patients suffering from MPDS as one of the first choices.

Key words: fluoxetine, clonazepam, myofacial pain dysfunction syndrome, depression.

INTRODUCTION

Myofacial pain dysfunction syndrome is the most frequent temporomandibular disorder (Manolopoulos, et al., 2008; Cardli, et al., 2005). This syndrome primarily influences the masticatory muscles (in 90% of cases) and leads to pain, limitation of jaw movement and functional disability, deviation of the midline on opening or closing, tenderness in one or more of masticatory muscles and tendons (Sherman, et al., 2001).

According to the Weinberg’s, the etiology of TMJ disorders can be divided into four classifications: stress, occlusion, condylar displacement within the fossae, and anterior displacement of the disk (Weinberg, et al., 1973). Some epidemiological studies suggest that 40 to 75 percent of general population may present at least one symptom during their life (Okeson, 1993). Women are more affected than men. Although occlusal and psychological disorders are more distinguished in these patients, studies have shown that only in 10 to 20 percent of cases, there is a causative relation between occlusal disorder and temperomandibular pain (Carlsson, et al., 1999).

The implication of stress as a part of psychiatric considerations for TMJ complaints was presented by (Moulton, 1955). Her investigation indicated that tension and emotional stresses increase the severity of the symptoms (Moulton, et al., 1955).

The role of stress in temporomandibular joint (TMJ) dysfunction syndrome has been confirmed in many researches (Akhter, et al., 2007; Yap, et al., 2002; Yap, et al., 2003; Reibmann, et al., 2008; Cascos-Romero, et al., 2009). In contrast, McGregor found no differences between depression rates in orofacial pain patients and normal controls (McGregor, et al., 1996).

Stressful events such as challenges in private and occupational life, financial problems, cultural and ethical differences all can play a trigger role in emanating pain and other symptoms of the disease (Akhter, et al., 2007; Yap, et al., 2002; Yap, et al., 2003; Reibmann, et al., 2008).

Stress and challenges, reduce the inhibitory effect of descendent sensory system located in thalamus, which results in depletion of GABA and endorphins in CNS, hyperactivity of efferent gamma neuron fibers, and consequently contraction and pain in the muscles.( Le´pine, et al., 2004)

Other studies have shown that patients suffering from MPDS are more vulnerable to the daily life problems with a considerable level of anxiety and depression (Akhter, et al., 2007; Yap, et al., 2003; Yap, et al., 2002)
Therapeutic goal consists of pain relief, reducing the abnormal masticatory pressure, and re-establishment of daily routines. Therefore, treatment is divided into two phases. The first phase includes educating the patients, stress and anxiety management drug therapy, physiotherapy, splint therapy. The second phase includes the occlusal adjustment, teeth reconstruction and orthognathic surgical therapies. (Manolopoulos, et al., 2008; Bennett, et al., 2007) (Syrop, et al., 2002) showed that performing first phase therapies perfectly can lead to 75 to 90 percent of success and Wahlund reported that adolescents with TMJ disorders reported more intense experiences to somatic stimuli (Syrop, et al., 2002; Walnut, et al., 2005).

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(Reddy, et al., 1994) have reported that Benzodiazepines, especially clonazepam and alperazolam, are the drugs of choice in muscular spasm coexisting with anxiety with chronic pains (Reddy, et al., 1994). Turp and Eisele suggested clonazepam, diazepam, amitriptyline, and meprobamate in the treatment of muscular pain dysfunction syndrome (Turp, et al., 2004; Eisele, et al., 1999).

The efficacy of fluoxetine in the treatment of depression, chronic pain, neuropathic pain, fibromyalgia, and even headache has been confirmed by many researchers such as Calil, Kusstarica, Rossi, Guri and others (Rossi, et al., 2004; Gury, et al., 1999; Calil et. al., 2001; Kusstarica, et al., 2002).

Clonazepam is a benzodiazepine derivative with anticonvulsant, muscle relaxant, and very potent anxiolytic properties (Robertson and Drummer, 1995). Clonazepam primarily affects modulating GABA function in the brain and benzodiazepine receptor which in turn leads to enhanced inhibition of neuronal firing. In addition clonazepam decreases the utilization of serotonin by neurons and has been shown to bind tightly to central type benzodiazepine receptors (Jenner, et al., 1986)

It is classified as a highly potent benzodiazepine because of its strong anxiolytic and anticonvulsant properties. The anticonvulsant properties of benzodiazepines are due to enhancement of synaptic GABA responses and inhibition of sustained high frequency repetitive firing (Gavish and Fares, 1985).

The study of Camoratto & Grandison on rats showed that Benzodiazepines act via micromolar benzodiazepine binding sites as Ca2+ channel blockers and significantly inhibit depolarization-sensitive calcium uptake in experimentation on brain cell components (Camoratto and Grandison, 1983).

Clonazepam binds to the benzodiazepine site of the GABA receptors and causes an enhancement of the electric effect of GABA binding on neurons. This results in an inhibition of synaptic transmission across the central nervous system (Taft and DeLorenzo, 1984). Clonazepam has no effect on GABA levels or on gamma-aminobutyric acid transaminase. Clonazepam does however affect glutamate decarboxylase activity (Varotto and Roman, 1981)

Fluoxetine (also known by the tradenames Prozac, Sarafem) is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class Fluoxetine is approved for the treatment of major depression (including pediatric depression), obsessive-compulsive disorder (in both adult and pediatric populations), bulimia nervosa, panic disorder and premenstrual dysphoric disorder (Denninger, et al., 2006).

Despite the availability of newer agents, fluoxetine remains extremely popular. It is an antidepressant in a group of drugs called selective serotonin reuptake inhibitors (SSRIs). Fluoxetine affects chemicals in the brain that may become unbalanced and cause depression, panic, anxiety, or obsessive-compulsive symptoms.

Fluoxetine is sometimes used together with another medication called olanzapine (Zyprexa) to treat depression caused by bipolar disorder (manic depression).

Clonazepam and Fluoxetine have the ability to facilitate the inhibitory effects of GABA, affects the amount of serotonin and adrenaline levels in synapses and inhibition of spinal multi-synaptic afferent pathways (Denninger, et al., 2006).

Regarding these evidences, and high rate of depression and anxiety in patients suffering from MPDS, clonazepam, and fluoxetine (selective serotonin re-uptake inhibitor) can be prescribed to control both anxiety and depression and MPDS symptoms.

METHODS AND MATERIALS

In this before-after study, 39 patients with clinical diagnosis of MPDS were treated with a combination of clonazepam and fluoxetine for a period of six months.

The study protocol was approved by the Institutional Ethics Committee (IEC) of Mashhad University, and each subject signed a detailed informed consent form.

The diagnosis was made by two oral medicine specialists on the basis of pain and tenderness in masticatory muscles (most important criteria) with or without limitation of mandibular opening, clicking of TMJ, deviation and deflection of the midline on opening and in the pain clinic.

Patients who had a history of seizure, cervical trauma or suffering from systemic and joint muscle disease were excluded from our study.

Patients who showed side-effects of either fluoxetine or clonazepam during the treatment were considered as a case of exclusion.
The patients’ pain experience was measured by means of the visual analogue scale (VAS) as follows: 0=no pain, 1 \leq \text{VAS} \leq 4 as mild pain, 4 \leq \text{VAS} \leq 7 as moderate pain, 7 \leq \text{VAS} \leq 9 as severe pain, and 10=very severe pain (Huskinsson, 1982; Price, et al., 1983).

Maximal painless mandibular opening was defined as the vertical distance between the upper and lower incisal edge of anterior teeth and measured with culis. According to Okeson index, the maximum painless mandibular opening is 40 mm, thus, lower results were considered as a limitation of mandibular opening (Okeson, 1996). Helkimo considered mandibular opening in the range of 30 to 39 mm as mild limitation, and lower than 30 as severe limitation (Helkimo, 1974). Changes in pain severity of masticatory muscles and maximal painless mandibular opening have been documented during six-month period through nine examinations.

The primary dose of clonazepam was 0.5 mg daily and prescribed twice a day. In order to reach the minimum effective dose of clonazepam for each patient, all of them have been visited weekly and the dose of drug was increased 0.25 mg weekly (up to maximum dose of 1.5 mg daily) in the case of no response (no changes in the level of pain or tenderness and maximal mandibular opening).

The same process was performed with fluoxetine, with a primary dose of 10 mg, which was increased 10 mg every three weeks up to maximum dose of 60 mg, in the case of lack of response.

Fluoxetine has been prescribed for six months and then tapered during one month. Clonazepam also has been tapered during two weeks after a five-week period of usage, because of the risk of dependency for clonazepam.

Our criteria for improvement was defined as total omitting of pain and tenderness in masticatory muscles (VAS=0). All these process were under supervision of a psychologist.

We have used descriptive statistics including mean, median, tables, and diagrams, and also inferential statistics including Students t-test and Wilcoxon. Kolmogrov-Smirnov test was also used to determine normal distribution of variables. Minitab software was used to analyze the data.

RESULTS AND DISCUSSION

MPD was more prevalent in females in our study (82.1%). The average age was 35 years (SD=13.3). The mean maximal mandibular opening was 35.4 mm (SD=7.01).

According to Okeson index, 71.8% (28 patients) were suffering from limitation of mandibular opening in the first visit before starting the treatment, and also 61.5% (24 patients) were suffering from mild limitation, and 10.3% (4 patients) from severe limitation (Helminko index).

Most of our patients (89.7%) were cured without any occlusal therapy. Table-1 illustrates the changes in pain severity during the nine visits and compares them with the first visit before starting the treatment, regarding the abnormal distribution of this variable showed by kolomogrov-smirnov test.

Tenderness of masticatory muscles was decreased gradually after starting the treatment.

Pain in palpation of TMJ was reported by 54% of patients at first visit that was completely improved after treatment course (Table-2). Changes in the range of painless mandibular opening and the efficacy of the treatment during nine visits have also been illustrated in table 3.

Kolomogrov-Smirnov test analyze and t. test revealed that maximal painless mandibular opening have been increased after the fourth visit (3 months). None of our patients reported side effects relating to these drugs. After the last examination, the average opening of the mouth was near normal value.

Discussion:

Our study revealed that the use of fluoxetine and clonazepam (regardless of psychological disorders) results to complete improvement in 90% of the patients, without performing any occlusional therapy.

It is clear that there is an association between pain feeling and depression. Indeed it has been suggested that painful symptoms might be an integral part of depression and that major depression should be considered as a disorder characterized by a triad of psychological, somatic symptoms and painful physical symptoms (Stahl, et al., 2002). It has been shown that chronic pain and depressive disorders share some common pathophysiology (Magni, 1990).

The clinical overlap of pain and depression has been explained with the anatomical coincidence of both nociceptive and affective pathways (Basbaum and Fields, 1978). Norepinephrine and serotonin, the two neurotransmitters most implicated in the pathophysiology of mood disorders, are also involved in the gate-control mechanism of pain (Lindsay and Olsen, 1985), and antidepressants have been found to have an effect on chronic pain (Lindsay and Olsen, 1985).

On the other hand, several studies have found that TMD correlates with some personality characteristics similar to those of other chronic pain patients (Michelotti, et al., 1998; Mongini, et al., 2000) while others have shown no evidence of any separate personality profile to be connected with TMD (Parker, et al., 1993; Marbach, 1995; Feinmann, 1996).
Myofacial pain dysfunction syndrome was more prevalent in females in this study that was in agreement with the findings of other researchers such as Yap, De Oliviera and Velly (Yap, et al., 2003; De Oliviera, et al., 2006; Velly, et al., 2003).

This may be related to lower tolerance of women to pain, more stressful life, and higher prevalence of psychological problems among them.

Limitation of mandibular opening is a frequent finding in MPDS, which has been noticed in 71.8% of our cases.

According to the result of this study, although the pain in masticatory muscles follows a downward trend after starting of the treatment, maximal painless mandibular opening had not been changed before the fourth visit, therefore, it is assumed that minimum length of time for improvement in the function and efficacy of masticatory muscles is 3 months and then efficacy of treatment will be more profound.

This study weakens the role of occlusion in the etio-pathogenesis of MPDS as 90% of our patients improve without any occlusal therapy.

The aim of this study was to achieve an effective treatment for MPDS without any occlusal treatment. Our study showed that 89.7% of our patients improved completely and the remaining unanswered patients referred to psychologists for further evaluation and treatments. Unfortunately none of these patients accepted to be referred to psychologist because they don't believe to have psychologic problems.

**Conclusion:**
This study suggest that common former therapies should be reconsidered, and the treatment of psychological problems seems to be the high priority, through which unnecessary, costly, and time-consuming therapies can be omitted.

Therefore, considering that no side-effect has been observed following the prescription of fluoxetine and clonazepam and the high efficacy of these drugs in treatment of MPDS, this regimen is suggested as the choice therapy.

**Table 1:** Changes in pain severity in recovered patients during the treatment.

<table>
<thead>
<tr>
<th>Pain severity</th>
<th>No. of patients</th>
<th>VAS min</th>
<th>VAS max</th>
<th>VAS mean</th>
<th>SD</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>before treatment</td>
<td>35</td>
<td>10</td>
<td>5</td>
<td>6.8286</td>
<td>1.20014</td>
<td>1.44</td>
</tr>
<tr>
<td>first visit (after treatment)</td>
<td>35</td>
<td>8</td>
<td>3</td>
<td>5.4000</td>
<td>0.97619</td>
<td>0.953</td>
</tr>
<tr>
<td>2nd visit</td>
<td>35</td>
<td>8</td>
<td>3</td>
<td>4.8857</td>
<td>0.05081</td>
<td>1.104</td>
</tr>
<tr>
<td>3rd visit</td>
<td>35</td>
<td>7</td>
<td>2</td>
<td>4.2000</td>
<td>0.07922</td>
<td>1.165</td>
</tr>
<tr>
<td>4th visit</td>
<td>35</td>
<td>6</td>
<td>2</td>
<td>3.5429</td>
<td>0.95001</td>
<td>0.903</td>
</tr>
<tr>
<td>5th visit</td>
<td>35</td>
<td>6</td>
<td>1</td>
<td>2.8857</td>
<td>0.05081</td>
<td>1.104</td>
</tr>
<tr>
<td>6th visit</td>
<td>35</td>
<td>3</td>
<td>1</td>
<td>2.3429</td>
<td>0.72529</td>
<td>0.526</td>
</tr>
<tr>
<td>7th visit</td>
<td>35</td>
<td>3</td>
<td>0</td>
<td>1.5143</td>
<td>0.91944</td>
<td>0.845</td>
</tr>
<tr>
<td>8th visit</td>
<td>35</td>
<td>3</td>
<td>0</td>
<td>0.6000</td>
<td>0.77460</td>
<td>0.600</td>
</tr>
<tr>
<td>9th visit</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>0.0000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

F.: Frequency

**Table 2:** Changes in pain severity in TMJ during the treatment.

<table>
<thead>
<tr>
<th>Visit after treatment</th>
<th>First</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>6th</th>
<th>7th</th>
<th>8th</th>
<th>9th</th>
</tr>
</thead>
<tbody>
<tr>
<td>pain</td>
<td>F.  %</td>
<td>F.  %</td>
<td>F.  %</td>
<td>F.  %</td>
<td>F.  %</td>
<td>F.  %</td>
<td>F.  %</td>
<td>F.  %</td>
<td>F.  %</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>14</td>
<td>67</td>
<td>16</td>
<td>76</td>
<td>18</td>
<td>86</td>
<td>18</td>
<td>86</td>
<td>19</td>
</tr>
<tr>
<td>moderate</td>
<td>7</td>
<td>33</td>
<td>5</td>
<td>24</td>
<td>3</td>
<td>14</td>
<td>3</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Very severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sum.</td>
<td>21</td>
<td>100</td>
<td>21</td>
<td>100</td>
<td>21</td>
<td>100</td>
<td>21</td>
<td>100</td>
<td>21</td>
</tr>
</tbody>
</table>

**Table 3:** Changes in maximum painless opening during the treatment.

<table>
<thead>
<tr>
<th>Range of PMO</th>
<th>Min.</th>
<th>Max.</th>
<th>mean</th>
<th>SD</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>First visit (A.T)</td>
<td>17</td>
<td>52</td>
<td>36.95</td>
<td>6.97</td>
<td>48.62</td>
</tr>
<tr>
<td>2nd visit</td>
<td>17</td>
<td>52</td>
<td>37.26</td>
<td>6.96</td>
<td>48.51</td>
</tr>
<tr>
<td>3rd visit</td>
<td>18</td>
<td>52</td>
<td>37.77</td>
<td>6.76</td>
<td>45.70</td>
</tr>
<tr>
<td>4th visit</td>
<td>20</td>
<td>52</td>
<td>38.59</td>
<td>6.80</td>
<td>46.30</td>
</tr>
<tr>
<td>5th visit</td>
<td>21</td>
<td>52</td>
<td>39.08</td>
<td>6.72</td>
<td>45.17</td>
</tr>
<tr>
<td>6th visit</td>
<td>21</td>
<td>52</td>
<td>39.63</td>
<td>6.93</td>
<td>47.98</td>
</tr>
<tr>
<td>7th visit</td>
<td>22</td>
<td>53</td>
<td>40.54</td>
<td>7.03</td>
<td>49.41</td>
</tr>
<tr>
<td>8th visit</td>
<td>22</td>
<td>54</td>
<td>41.69</td>
<td>7.12</td>
<td>50.74</td>
</tr>
<tr>
<td>9th visit</td>
<td>22</td>
<td>55</td>
<td>42.23</td>
<td>7.06</td>
<td>49.81</td>
</tr>
</tbody>
</table>

PMO: painless mandibular opening A.T: after treatment
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