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Efficacy of Fixed Dose Combination of Chlorzoxazone, Aceclofenac and Paracetamol Versus Thiocolchicoside and Aceclofenac in Myofascial Pain Syndrome: A Randomised Clinical Study

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ABSTRACT

Objective: **To evaluate the comparative efficacy fixed dose combination (FDC) of chlorzoxazone, aceclofenac and paracetamol versus thiocolchicoside and aceclofenac in Myofascial Pain Syndrome (MPS) patients.**

Material and Methods: **This randomized controlled study was completed on 62 patients with the clinical diagnosis of MPS. Patients were randomly divided into two groups. Group A received FDC of chlorzoxazone (500 mg), aceclofenac (100 mg) and paracetamol (325 mg) and Group B received a FDC of thiocolchicoside (4 mg) and aceclofenac (100 mg), twice a day for one week. The response of the treatment was be assessed by VAS Scale) and Modified Severity Symptom Index (Mod SSI) questionnaire. Data was analyzed with Mann-Whitney U test and Wilcoxon matched pairs tests.**

Results: **The reduction in pain scores was significantly higher in thiocolchicoside and aceclofenac group as compared to chlorzoxazone, aceclofenac and paracetamol group, after 4 days and 7 days from baseline. Further, a significant difference was observed between baseline to 4 day, baseline to 7 days with pain (VAS) scores in Group A and Group B groups.**

Conclusion: **In this study, FDC of thiocolchicoside and aceclofenac in patients with MPDS was proved to be slightly more effective and without any significant side-effects as compared to FDC of chlorzoxazone, aceclofenac and paracetamol.**

KEY WORDS

myofascial pain syndrome, visual analog scale

INTRODUCTION

Myofascial pain syndrome is one of the most common causes of chronic pain in the musculoskeletal system. It was believed to arise due to sensitive areas in a muscle that spontaneously or on compression causes pain to a distant region. MPS is known to have mutifactorial etiology including deranged occlusion, bruxism, increased pain sensitivity, stress and anxiety. The hyperactivity of the muscles and muscular dysfunction secondary to malocclusion are known to be the responsible factors for the clinical manifestations. Degenerative joint disorders, rheumatoid arthritis, ankylosis, dislocation, infection, tumors and developmental anomalies are the factors that cause pain and tenderness. According to a psychophysiologic theory, musclular spasm is the prome factor for myofascial pain dysfunction syndrome. It has been also proposed that, apart from mechanical factors emotional factors could be the prime causes in stimulating chronic oral habits that produce muscle fatigue[1,2)].

MPS has been recognized as the most common, non tooth-related chronic orofacial pain condition that confronts dental practitioners. The

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Table 1: Comparison of Group A and Group B with respect to pretest and posttest pain (VAS) scores at baseline, 4 days and 7 days by Mann-Whitney U test

Groups	Baseline		4 days		7 Days		Changes from baseline to			
							4 days		7 Days	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Group A	6.2	1.3	4.8	1.3	3.3	1.5	1.4	0.5	2.9	0.7
Group B	7.3	0.9	4.5	0.8	2.4	0.8	2.8	0.9	4.9	0.7
% of change in Group A							22.58%#, p = 0.0050*		46.77%#, p = 0.0049*	
% of change in Group B							38.36%#, p=0.0050*		67.12%#, p=0.0047*	
Z-value	-1.8684		-0.8240		-1.3773		-3.2238		-3.6430	
P-value	0.0617		0.4099		0.1684		0.0013*		0.0003*	

*p < 0.05, #applied Wilcoxon matched pairs test

Table 2: Comparison of Group A and Group B with respect to pretest and post test CGS (Pain) scores by Mann-Whitney U test

Groups	Pretest		Posttest		Changes from pretest to posttest	
	Mean	SD	Mean	SD	Mean	SD
Group A	59.09	10.48	53.58	11.03	5.51	2.82
Group B	69.14	6.76	56.80	8.48	12.35	6.32
% of change in Group A					9.33%#, p = 0.0051*	
% of change in Group B					17.85%#, p = 0.0050*	
Z-value	-2.1922		-0.4536		-2.9114	
P-value	0.0284*		0.6502		0.0036*	

*p < 0.05, #applied Wilcoxon matched pairs test

management of MPS requires a prolonged approach. In the short term, eliminating taut bands and tender spots for pain relief are the main objectives[3]. In long term, achieving muscle flexibility and eliminating precipitating factors are the objectives. A multi disciplinary approach is used for the treatment of MPDS which includes counseling to discontinue any parafunctional habit, physiotherapy and ultrasound therapy[4].

Current trends in management of MPS addresses a conservative approach such as incorporation of exercise, soft diet, massage therapy, acupressure, acupuncture, application of cold and moist heat, TENS therapy, ultrasound, spray therapy and physiological treatment[5].

With respect to medications NSAID's and skeletal muscle relaxants are used in managing the pain related with MPS. NSAID's provides a temporary relief but does not reduce the discomfort secondary to the muscle spasticity and in such cases, centrally acting or peripherally acting drugs can be administered[6]. Unfortunately NSAIDs have gastric intolerance, whereas most of the centrally acting muscle relaxants have central nervous system depressant side-effects such as sedation, dizziness, impairment of co-ordination, mental confusion, weakness etc[7]. Hence, these limiting factors demands a need for an ideal fixed dose combination which is devoid of effects on psychomotor performance, free of sedation and higher tolerability. Centrally acting drug chlorzoxazone is routinely indicated for lower back pain and in other similar conditions related to orthopaedics[8].

Thiocolchicoside is a semi-synthetic derivative of colchicines, a natural glycoside originated from flower seeds of superbagloriosa. It has an affinity for the inhibitory glycine and Gamma-aminobutyric acid (GABA)-A receptors i.e., have glycomimetic and gaba mimetic activity, therefore shows muscle relaxant action. As it has GABA-mediated action, so it shows both myorelaxant as well as analgesic activity. It has demonstrated its clinical efficacy and safety in many clinical trials. It has also been reported that thiocolchicoside produces muscle relaxation without any subjective or objective sedative side-effects[7]. Till date no study compared efficacy of two FDCs of chlorzoxazone, aceclofenac and paracetamol versus thiocolchicoside and aceclofenac in MPS patients, hence the present study was undertaken to compare the efficacy and safety of the both FDCs in patients with MPS.

MATERIALS AND METHODS

Study design

This prospective, randomized, comparative drug study was after obtaining the approval by the institutional review board. Subjects of either gender with complaint of pain in the temporomandibular joint region and one or more masticatory muscles reporting to the Out Patient Department were incorporated in this study after obtaining informed consent. Patients aged between 18 to 45 years with MPS according to Research Diagnostic Criteria of Temporomandibular Disorders were included in the study[8]. Chief complaints of patients were mostly diffuse pain upon waking and/or aggravated by mandibular movements. The duration of pain in all patients was less than three months at the time of inclusion in this study. Pain response to palpation of the masticatory muscles was positive.

The exclusion criteria was as follows

- Patients diagnosed with other TMJ disorders such as, fractures, arthralgia, fibromyalgia and rheumatoid arthritis.
- If patient is under treatment for anti-depressants or alcohol.
- Pregnant and lactating women
- History of presence of gastrointestinal disorders like peptic ulceration or gastrointestinal bleeding or severe dyspepsia
- Patients allergic to NSAIDs and skeletal muscle relaxants
- Patients suffering from asthma or other allergic disorders
- Patients treated with NSAIDs or skeletal muscle relaxants for 3 days before the study
- Patients with severe concurrent systemic disease including bleedings diathesis,
- Patients on anticoagulation therapy
- Patients with history of liver and kidney disorders
- Patient who were unwilling to participate

Sample size calculation

For the present study, the sample size was estimated using G*power 3.0.1. The power (1-β) of the study was set at 0.8, and the type I error rate (α) was set at 0.05, and medium effect size of 0.5. Using the above parameters, the total sample size was calculated as 62.

Treatment

Patients of either gender between 20 years and 60 years of age were randomly assigned to Group A and Group B comprising 31 patients

each. The randomization was carried out by casting lots by an individual not participating in this study to allocate the subjects to either group. Group A received FDC of chlorzoxazone (500 mg), aceclofenac (100 mg) and paracetamol (325 mg) and Group B received a FDC of thiocolchicoside (4 mg) and aceclofenac (100 mg). Both the FDCs were prescribed orally, twice a day for one week.

Clinical evaluation

The primary outcome measures of the treatment were regarded as a decrease in pain. The severity of pain and dysfunction were measured with visual analog scale [VAS] the scores ranged from 0 (no pain) to 10 (extreme pain) and Modified Severity Symptom Index (Mod SSI) questionnaire[9].

Side-effects such as tiredness, drowsiness, dizziness and alertness were noted based on history, observations of adverse reactions. Readings were noted on day 1 (baseline), 3rd day and 7th day

Statistical Analysis

Data was analyzed by using SPSS 21.00 version statistical software with Mann-Whitney U test and Wilcoxon matched pairs tests. The statistical significance was set at 5% level of significance ($p < 0.05$).

RESULTS

In Group A, there were 17 (54.83%) females and 14 (45.17%) males with the mean age of 32.91 ± 12.57 years, and the Group B comprised of 18 (58.06%) females and 13 (41.94%) males with the mean age of 36 ± 1.2 years.

From the results of the table 1, it can be seen that, no significant difference was observed between Group A (6.2 ± 1.3) and Group B (7.3 ± 0.9) with baseline pain (VAS) scores ($Z = -1.8684$, $p > 0.05$), Group A (4.8 ± 1.3) and Group B (4.5 ± 0.8) with 4 days pain (VAS) scores ($Z = -0.8240$, $p > 0.05$) and Group A (3.3 ± 1.5) and Group B (2.4 ± 0.8) with 7 days pain (VAS) scores ($Z = -1.3773$, $p > 0.05$). But a significant difference was observed between Group A (1.4 ± 0.5) and Group B (2.8 ± 0.9) with changes of pain (VAS) scores from baseline to 4 days ($Z = -3.2238$, $p = 0.0013$). Similarly, a significant difference was observed between Group A (2.9 ± 0.7) and Group B (4.9 ± 0.7) with changes scores of pain (VAS) scores from baseline to 4 days ($Z = -3.6430$, $p = 0.0047$). It implied that, the reduction in pain scores significantly higher in Group B as compared to Group A after 4 days and 7 days from baseline. Further, a significant difference was observed between baseline to 4 day, baseline to 7 days with pain (VAS) scores in Group A and Group B groups (17.85% reduction).

A significant difference was observed between Group A (59.09 ± 10.48) and Group B (69.14 ± 6.76) with pretest CGS (pain) scores ($Z = -2.1922$, $p = 0.0284$). But a non-significant difference was observed between Group A (53.58 ± 11.03) and Group B (56.80 ± 8.48) with posttest CGS (pain) scores ($Z = -0.4536$, $p = 0.6502$). Similarly, a significant difference was observed between Group A (5.51 ± 2.82) and Group B (12.35 ± 6.32) with changes scores of CGS (pain) scores from pretest to posttest ($Z = -2.9114$, $p = 0.0036$). This suggested that, the reduction in CGS (pain) scores significantly higher in Group B as compared to Group A after posttest. Further, a significant difference was observed between pretest and posttest CGS (pain) scores in Group A (9.33% reduction) and Group B groups (17.85% reduction) (Table 2).

The side-effects reported during study period showed a statistically significant ($P < 0.0001$) better safety profile in the Group B when compared with Group A. None of patient reported with sedation, drowsiness or dizziness and only two patients out 31 (6.45%) manifested gastrointestinal side-effects during the study treated in the Group B, while in Group A, 21 (67.74%) patients reported with sedation, drowsiness or dizziness and 12 patients (38.7%) manifested gastrointestinal side-effects.

DISCUSSION

Masticatory muscle spasm and tenderness is one of the most common presenting features of the MPS, which can limit the jaw movements leading to a compromise in quality of life of the patients with an abrogating impact on social function and emotional health[11].

The success for a treatment of any disorder relies on two considerations: relieving of symptoms and treating the cause. In this view, various treatment modalities for TMD have been tried and tested over time. Choosing a specific conservative treatment modality for MPDS patients depends on clinicians expertise, patient presentation, and elimination of possible etiologic factors. Till date, no single treatment modality has been proven to be better than any other for TMD.

A wide assortment of remedial methodology, for example, medicinal treatment, occlusal splints, physical therapy, orthodontic therapy, and so on, have been utilized to limit the pain in individuals with MPS. Still there is shortage of randomized controlled clinical studies, to recommend suitable management protocol of these subjects. Albeit different treatments seem to bring about comparable recovery in pain and dysfunction, discretion is needed concerning implementation of invasive and other irreversible therapies[5].

Nonsteroidal anti-inflammatory analgesics (NSAIDs) are known to be effective in the management of mild-to-moderate inflammatory conditions, particularly of the musculoskeletal system[12]. Muscle relaxants are administered to reduce skeletal muscle tone and are often administered to patients with muscle tone and chronic orofacial pain to help prevent or alleviate the increased muscle activity[12]. They are thought to decrease muscle tone without the impairment of motor function by acting centrally to depress polysynaptic reflexes.

Naikmasur *et al*., noted significant improvements in symptoms related to MPDS after administering FDC of ibuprofen 400 mg, paracetamol 325 mg, and chlorzoxazone 250 mg for a period of 5 to 7 days. Four patients in their study reported mild gastrointestinal symptoms during the follow-up, which resolved after the discontinuation of the medications[13].

Lahoti observed in patients with low back pain that FDC of aceclofenac, thiocolchicoside and paracetamol significantly minimized the intensity of pain and improve the mobility[13]. Similarly, Kumar *et al*., noted that administration of FDC of thiocolchicoside (4 mg) and aceclofenac (100 mg) twice a day for one week reduced the pain and muscle spasm in patients with low back pain and there were no notable side-effects reported[7].

Anitha *et al*., in their study, noted a statistically significant better safety profile in subjects who were administered FDC of tthiocolchicoside, aceclofenac and paracetamol. The authors recommended FDC of thiocolchicoside, aceclofenac and paracetamol as a preferred option for treating the patients with lower backache pain associated with muscle spasm[15].

In a multicenter, prospective, open-labeled study, fixed-dose combination of aceclofenac (200 mg) and thiocolchicoside (8 mg) in patients with acute inflammatory conditions associated with muscle spasm once daily for 2 weeks. The authors noted a significant pain reduction without any serious adverse effects and concluded that the FDC is well tolerated in the treatment of patients with acute musculoskeletal inflammatory conditions[16].

In a prospective observational study patients with low back pain were administered a combination of aceclofenac and thiocolchicoside and compared with patients receiving aceclofenac only. The authors noticed a decrease in severity of pain was was more pronounced within patients receiving aceclofenac and thiocolchicoside as compared to patients receiving aceclofenac therapy[17].

After observing the promising results of FDC of thiocolchicoside and aceclofenac in the above mentioned studies, we decided to assess the efficacy of this FDC in MPDS patients.

We recommend that further studies in should be carried out in multiple centers involving larger samples may help to validate and generalize the results seen in the present study.

CONCLUSION

In this present randomized prospective study, FDC of thiocolchicoside and aceclofenac in patients with MPDS was proved to be slightly more effective and without any significant side-effects as compared to FDC of chlorzoxazone, aceclofenac and paracetamol.

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