INTRODUCTION

Temporomandibular disorders (TMD) is a collective term used to describe a number of related disorders affecting the temporomandibular joints, masticatory muscles, and associated structures, all of which have common symptoms such as pain and limited mouth opening.\(^1\) TMDs affect 5–10% of the population. Individuals may have TM joint pain, ear ache, headache, clicking and popping sounds, and alteration in jaw movements. Excluding myofacial pain and alteration in jaw movements, patients with TMD may exhibit enhanced pain sensitivity and psychological dysfunction as a result of impairment in CNS mediated regulatory processes.\(^2\)

The etiology of TMD is complex, unclear but multifactorial. Several risk factors including trauma to the TMJ area, anatomical factors, psychosocial profile, and sensitization of pain carrying neural pathways plays a vital role in causation of TMD.\(^2\) Studies involving twins and family members have suggested the genetic foundation behind TMDs. Moreover, physical, psychosocial and emotional stress with altered adrenergic receptor mediated responses can increase the probability of developing TMD. Modern lifestyle and sedentary jobs, modern work culture brings stress into spotlight. Further, the treatment outcomes in TMD patients are found to be largely influenced by psychological factors. Therefore, TMDs...
are known as a group of “biopsychosocial illnesses” characterized by chronic painful conditions and dysfunctions in the muscles of mastication and TMJ.[2]

Detailed patient’s history, an accurate physical examination and quantification of pain on a graded scale are an integral part in diagnosing as well as treating TMD.[3] These include recording the maximal interincisal mouth opening, palpation of masticatory muscles, auscultation of joint noises and mandibular function appraisal (i.e., opening and lateral movements of jaw bone) as well as detailed examination of occlusion.[4]

Patient education and self care is essential in alleviating pain associated with TMD. This includes restricting mandibular function and stress, home exercise course, habit awareness and modification. One should voluntarily limit mandibular function to provide rest/immobilization to articular and muscular structures. This can be accomplished by chewing soft foods, avoiding activities that may cause excessive jaw movements like wide yawning, singing, chewing gum.[6]

Non-surgical treatment of TMDs continues to be the more effective way of managing patients. NSAIDs have been the mainstay in pain management. Muscle relaxants are known to be efficacious in alleviating myalgia. Skeletal muscle relaxants are classified into two: antispastic and antispasmodic medications. Antispastic agents work on the spinal cord or directly on the skeletal muscles to improve muscle hypertonicity and involuntary spasms whereas antispasmodics decrease muscle spasms through alterations of CNS conduction.[7] Chlorzoxazone is an antispasmodic agent that is indicated for symptomatic treatment of muscle spasms and pain associated with musculoskeletal conditions like myalgia. The dearth of clinical trials on efficacy of adding a muscle relaxant to NSAIDs prompted the initiation of this study.

The present study was conducted to evaluate and compare the efficacy of topical and systemic NSAIDs in the management of TMD. The study divided the participants into 4 categories: GROUP 1: oral diclofenac 50 mg, GROUP 2: oral diclofenac 50 mg, paracetamol 325mg with chloroxazone 500mg and GROUP 3: topical diclofenac gel topical application thrice daily for 7 days. GROUP 4: 200mg diclofenac transdermal patch applied for 8-12 hrs for 7 days.
AIM
To evaluate the efficacy of 4 different NSAIDs in treating muscular pain resulting from TMD.

OBJECTIVES
1. To compare the efficacy between topical and systemic medications.
2. To evaluate whether the addition of a compound (muscle relaxant) in systemic medication is synergistic in alleviating pain.

MATERIAL AND METHOD
A single blinded cross-sectional study was conducted from Jan 2015 to Nov 2015 in the Department of Oral Medicine and Radiology and a total of 80 clinically diagnosed cases of TMDs of muscular origin were selected. All the relevant information regarding demographic data, detailed history and clinical findings were recorded in a structured proforma after taking a written informed consent for the clinical drug trial. Detailed examination of muscles of mastication and accessory muscles are an integral part of identifying the source of pain.

Inclusion criteria were as follows
(i) Patients with signs and symptoms of muscular pain of TMD origin according to the Research Diagnostic Criteria for Temporomandibular Disorder (RDC-TMD).[7]
(ii) Subjects who are in a fit state of mind to answer the questionnaire

Exclusion criteria include the following
(i) Subjects with history of connective tissue disorders or systemic conditions which may affect the functioning of TMJ for e.g., rheumatoid arthritis, scleroderma, and septic arthritis.
(ii) Subjects with any co-morbid conditions like hypertension, diabetes, asthma, epilepsy.
(iii) Subjects who had a history of treatment for TMD in the past;
(iv) Subjects with any history of malignancy of the maxillofacial area.
(v) Subjects with history of gastritis or peptic ulcer.

Once the diagnosis of myalgia due to TMD was made, the patients were randomly allocated in one of the treatment groups. The study divided the participants into 4 categories:
GROUP 1: oral diclofenac 50mg REACTIN-50® (Cipla Pharma limited) twice daily for 7 days,

GROUP 2: oral diclofenac 50mg, paracetamol 325mg with chloroxazone 500mg CIP-ZOX® (Cipla Pharma limited) twice daily for 7 days and

GROUP 3: topical diclofenac gel COFENAC gel® (Cipla Pharma limited). Topical application thrice daily for 7 days to the muscle with gentle application avoiding long manipulation in the form of massaging.

GROUP 4: 200mg of transdermal patch NUPATCH® (Zydus Candila Limited) to be applied over the trapezius muscle for 8-12 hours for 7 days.

Before the commencement of the study a written consent was taken from each participant. Patients were instructed to write a daily dairy to record their VAS score twice/thrice a day on 0, 3rd, 7th, 9th, 15th, 30th, 40th days which constituted the subjective assessment.

Patients were recalled on 3rd and 7th day. Drugs were discontinued after 7th day; subjective assessment (pain on VAS and maximal mouth opening) was done on follow up visits on 15th, 20th, 30th and 40th days.

RESULTS
A total of 80 patients were treated out which 44 (55%) were male and 36 (45%) were female. (Table 1) The mean age of the patients in Group 1 was 33.00 ± 12.08 years, Group 2; 32.25 ± 12.53 years, Group 3; 30.10 ± 13.55 years and Group 4; 30.35 ± 11.43 years. (Table 2).

Mann Whitney Test revealed the difference in pain intensity in each group from 0th (baseline) day to 7th day. Pain on VAS, at the end of 7th day, showed least score in Group 2 (Diclofenac+MR) and maximum score in Group 3 (Diclofenac gel) at p<0.05. Pain intensity on VAS showed similar score between Group 1 (Diclofenac Tablet) and Group 4 (Transdermal Diclofenac patch). (Table 3) Follow up conversation of 40th day yielded similar results. Unfortunately, 3 patients dropped out before the completion of the study.

Functional limitation which was measured by range of motion (ROM) showed best restoration in Group 2, least with Group 3 and comparable with Group 1 and 4. (Table 4).

Feedback on side effects pertaining to each analgesic was recorded. Two patients in Group 1 (Diclofenac tablet) and only 1 patient in Group 2 reported GIT symptoms.
Table 1: Gender wise comparison of study groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Gender</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male n (%)</td>
<td>Female n (%)</td>
</tr>
<tr>
<td>Diclofenac tablet</td>
<td>11 (55%)</td>
<td>09 (45%)</td>
</tr>
<tr>
<td>Diclofenac+muscle relaxant tablet</td>
<td>10 (50%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Diclofenac gel</td>
<td>11 (55%)</td>
<td>09 (45%)</td>
</tr>
<tr>
<td>Transdermal Patch</td>
<td>12 (60%)</td>
<td>08(40%)</td>
</tr>
<tr>
<td>Total</td>
<td>44(55%)</td>
<td>36(45%)</td>
</tr>
</tbody>
</table>

$\chi^2 = 0.404, P = 0.939 (>0.05)$, Not Significant Difference

Table 2: Age wise comparison of study groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (Years, Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac tablet (n= 20)</td>
<td>33.00 ± 12.08</td>
</tr>
<tr>
<td>Diclofenac+muscle relaxant tablet (n= 20)</td>
<td>32.25 ± 12.53</td>
</tr>
<tr>
<td>Diclofenac gel (n= 20)</td>
<td>30.10 ± 13.55</td>
</tr>
<tr>
<td>Transdermal Patch (n=20)</td>
<td>30.35 ± 11.43</td>
</tr>
</tbody>
</table>

Kruskal Wallis Test, P > 0.05, Not Significant Difference

Table: 3 Comparison of study groups for pain at different time intervals.

<table>
<thead>
<tr>
<th></th>
<th>Pain (VAS, Mean ± SD)</th>
<th>Kruskal Wallis Test ($\chi^2$)</th>
<th>Mann Whitney U test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diclofenac tablet</td>
<td>Diclofenac+muscle relaxant</td>
<td>Transdermal Patch</td>
</tr>
<tr>
<td></td>
<td>(n= 20)</td>
<td>tablet (n= 20)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.75 ± 1.59</td>
<td>6.30 ± 1.66</td>
<td>5.00 ± 1.90</td>
</tr>
<tr>
<td>1st Day</td>
<td>3.65 ± 1.60</td>
<td>3.40 ± 1.73</td>
<td>4.05 ± 0.60</td>
</tr>
<tr>
<td>2nd Day</td>
<td>2.15 ± 1.35</td>
<td>1.15 ± 1.27</td>
<td>3.35 ± 1.39</td>
</tr>
<tr>
<td>3rd Day</td>
<td>1.15 ± 0.93</td>
<td>0.25 ± 0.72</td>
<td>1.05 ± 1.97</td>
</tr>
<tr>
<td>4th Day</td>
<td>1.10 ± 0.85</td>
<td>0.10 ± 0.31</td>
<td>1.02 ± 0.98</td>
</tr>
<tr>
<td>5th Day</td>
<td>0.90 ± 0.72</td>
<td>0.10 ± 0.31</td>
<td>0.91 ± 0.63</td>
</tr>
<tr>
<td>6th Day</td>
<td>0.85 ± 0.67</td>
<td>0.05 ± 0.22</td>
<td>0.88 ± 0.75</td>
</tr>
<tr>
<td>7th Day</td>
<td>0.60 ± 0.68</td>
<td>0.10 ± 0.31</td>
<td>0.70 ± 0.47</td>
</tr>
</tbody>
</table>

Diclo gel > Patch > Diclo tab > Diclo+MR
Table: 4. Range of motion on follow up days.

<table>
<thead>
<tr>
<th>DAY</th>
<th>Mean Range of motion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td>3rd Day</td>
<td>33.0±6.76 mm</td>
</tr>
<tr>
<td>7th Day</td>
<td>37.4±7.45 mm</td>
</tr>
<tr>
<td>15th Day</td>
<td>37.2±4.56 mm</td>
</tr>
</tbody>
</table>

DISCUSSION

Effective pain control with least possible adverse effects (AE), used in lowest effective dosage, of analgesics should be the principle that a practitioner follows in pain management which is strongly attested by the FDA. In the present study, effective pain control was best achieved with Diclofenac with Chlorzoxazone. The overall evaluation pointed however, that the patch group seemed to be most benefitted as the control of pain was effective with least GI effects.

Diclofenac is an NSAID of aryl-acetic group that inhibits synthesis of proinflammatory prostaglandins (PGs) by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). It is more potent in inhibiting COX 2 than COX 1 enzymes as they have high selectivity for COX 2. The plasma half life is approx 2 hours and is well absorbed orally. Peripheral sensitization is an important target for pain pharmacology and this drug reduces the prostaglandin production by inhibiting the activity of cyclooxygenase enzymes. Therapeutic efficacy of this drug is high because of its high tissue penetrability maintaining its concentration at sites of inflammation.

Chlorzoxazone is a centrally acting muscle relaxant which is a congener of mephanesin. Mephanesin acts by depressing spinal internuncial neurones which modulates polysynaptic reflexes that contributes in the regulation of muscle tone. Though not associated with many side effects, it still needs to be administered with caution as it is known to cause drowsiness, light-headedness, and GI disturbances.

Drawing increased attention to the modality of alleviating pain is the topical or local application which comes in the wake of increased incidences of GI and CVS effects in conventional pain ameliorators. The main objective behind this targeted drug delivery is to reduce the systemic absorption which eventually limits drug toxicity. Numerous topical NSAIDs preparations have been developed like diclofenac gel, piroxicam gel/cream, ibuprofen gel. Topical gels act effectively if there is proper penetration into deeper tissue...
layer which is facilitated by dermis of skin rich in hydrophobic proteoglycans, dense capillary bed and lymphatic network that allows uptake of water soluble medications; however they first need to penetrate the lipophilic corneal layer. Hence, a topical agent must have optimal hydrophobic and hydrophilic properties; NSAIDs are usually lipophilic compounds.\textsuperscript{[12]} Optimal/desired molecular weight has been stated to be less than 500 Da;\textsuperscript{[12]} topical NSAIDs result in high drug concentration in muscle, which may be the contributor of pain reduction. Site of application may be an important variable in pain reduction. An added benefit was reduction in hepatic enzyme elevation incidence as compared to systemic drugs.\textsuperscript{[12]} The severity in GI effects was least in this group of subjects.

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream.\textsuperscript{[13]}

The transdermal “Nupatch” is an extremely potent pain relieving medicament which provides a sustained and continuous release of the drug. The working principle of a transdermal patch can be elaborated by its constituent elements namely polymeric matrix, drug, adhesive layer, permeation enhancers, backing laminate and release liner.\textsuperscript{[13]}

Polymeric matrix is the backbone and controls the release of the drug. Permeability enhancers are incorporated to increases the permeability of the drug, adhesive layer is given to ensure its position at site of application.\textsuperscript{[13]} This role is fulfilled by diethylamine compound. The backing laminate protects the patch from damage,\textsuperscript{[14]} it is present at the top, in the form an impermeable backing membrane that prevents the leaching of drug. It is usually designed to be applied at the site of inflammation for 8-12 hours. Supreme advantage of being spared of “first pass metabolism” in addition to negligible GI and CVS adverse effects, makes this a prime candidate as a muscular pain reliever,\textsuperscript{[13-15]} notwithstanding the fact that the patient is unable to take tablets orally.

A number of studies have established equal efficiency of use of a patch with systemic administration diclofenac.\textsuperscript{[15-18]}

**CONCLUSION**

Diagnosis and amelioration of pain continues to be one of the most commonly encountered clinical situations for health care worker. The most efficacious pharmacon is, not only the one that reduces the pain early, but with minimum fall out effects.
This study concludes that the use of analgesic patch is very effective as a pain ameliorator, one almost matching the effects of oral route, with added advantage of “step down” in GI disturbance. Doubtlessly, addition of a muscle relaxant has its superiority in terms of pain relief, albeit causation of CNS effects make is less desirable. The ease in use as well as a sustained and streamlined delivery of the mendicant to the muscle greatly enhances its counteractive effect against pain. Topical agents definitely seem to have a scope where AE is primary concern as it does considerably lowers pain, though slower and to a lesser extent.

REFERENCES


