ORIGINAL ARTICLE

Pharmacological Management of Temporomandibular Joint Dysfunction Syndrome: Non-steroidal Anti Inflammatory Drugs Vs Muscle Relaxants

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OBJECTIVE: The objective of this study is to assess the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDS) ibuprofen 400 mg and muscle relaxants, oral diazepam 5mg, for the management of temporomandibular joint dysfunction syndrome in middle aged (20-50 years) males and females.

METHODOLOGY: This randomized control trial was conducted in Oral and Maxillofacial Surgery Department at Riphah International University, Islamabad, Pakistan. After obtaining written consent, Patient information was recorded using performas and pre-operative orthopantomograms (OPG) to rule out TMJ pathologies. Pre-operative and post-operative symptoms of patients were measured with Visual Analog Scale and Vernier Callipers. Nonparametric permutation testing with bootstrapping was applied, along with data visualization, to reveal differences in post operative improvements for both drugs.

RESULTS: Oral diazepam and Ibuprofen were administered across a similar age range. The two medications were equally represented with no significant difference in gender distribution. comparison of pre- and post-operative mouth opening reveals a significant improvement for patients using Oral diazepam (Wilcoxon signed-rank test, ($p = 0.02$), indicated by an asterisk (*). In contrast, Ibuprofen did not exhibit a significant improvement in mouth opening (($p = 0.45$). Oral diazepam exhibited a substantial decrease in postoperative pain (($p = 0.001$)), which is also indicated by an asterisk (*). Ibuprofen, on the other hand, demonstrated an improvement, albeit without statistical significance (($p = 0.12$). Oral diazepam patients exhibited a broader range of pre- and post-operative mouth opening values across ages, despite the absence of significant trends between age and mouth opening. These findings emphasize that Oral diazepam is associated with substantially greater improvements in both pain reduction and mouth opening compared to Ibuprofen, rendering it a more effective treatment in the cohort under investigation.

CONCLUSION: The findings prove the efficacy of oral diazepam over ibuprofen and lead to better pharmaceutical management of patients with temporomandibular joint dysfunction syndrome.

CLINICAL RELEVANCE: Muscle relaxants relieve jaw stiffness and arrest the cycle of discomfort by focusing on muscle tension, spasm, and bruxism. Muscle relaxants help improve the quality of sleep which is particularly helpful for people with nocturnal bruxism.

KEYWORDS: Temporomandibular joint, post-operative pain, pharmacological management, ibuprofen, diazepam

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INTRODUCTION

Temporomandibular disorder (TMD) is a complicated condition which affects the temporomandibular joint (TMJ) as well as the associated musculoskeletal and neuromuscular structures of the head and neck.[1-4] The temporomandibular joint (TMJ) is a complex synovial joint, which lies between the glenoid fossa of the temporal bone and the condylar head of mandible. It facilitates intricate movements of the mandible in conjunction with masticatory muscles.[1-5] Population-based studies indicate that TMD is prevalent among 10–15% of adults, yet only about 5% seek treatment.[6,7] The highest incidence occurs during the ages of twenty and forty years, with a female-to-male proportion of around 4:1.[7-10]

Temporomandibular joint disorders (TMDs) are characterized by pain and functional impairment of the TMJ

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and masticatory muscles.[7] Aetiology is multifactorial, involving local injuries and systemic factors such as biological, environmental, social, emotional, and cognitive triggers. Physical factors like traumatic secondary synovitis, infection, and irritation may also contribute. Psychogenic factors, trauma, and malocclusion are some of the aggravating factors. Certain individuals with genetic predispositions may develop pain and dysfunction after acute trauma.[8] Effective treatment includes addressing contributing factors such as stress, depression, and oral parafunctional behaviours including bruxism and grinding.[11,12] Other associated factors include fibromyalgia, chronic headaches, psychiatric illnesses, sleep apnoea, and occlusal wear from teeth grinding and clenching. Integrating these elements into treatment plans is essential for effective management.[13] Common conditions associated with TMD include myofascial pain disorder, disk derangement, osteoarthritis, and autoimmune disorders, leading to a broader spectrum known as temporomandibular joint dysfunction syndrome (TMJDS).

TMJDS is a significant cause of nondental pain in the orofacial region.[6] Symptoms range from mild discomfort to debilitating jaw pain, typically localized in the preauricular area, limited range of mouth opening and/or lateral excursions, along with TMJ sounds described as popping, clicking, grating, or crepitus.[14-16] Moreover, TMJDS can lead to additional comorbidities, including headaches, sleep disturbances, and psychological distress, underscoring the need for effective therapeutic approaches. It is a prominent cause of nondental distress in the orofacial area. They are generally categorized into four categories: temporomandibular joint disorders, masticatory muscle disorders, headache disorders linked to TMJDS, and disorders affecting associated tissues, for example coronoid hyperplasia.[17,18]

Most patients with TMJDS improve through a combination of non-invasive therapies; however, management includes minimally invasive muscular and articular injections and surgery as well.[19-22] Reassurance, self-care education, cognitive behavioural therapy, and physical therapy are various forms of non-invasive treatment modalities.[14,19,23] Conservative options like acupuncture, psychotherapy, and splint therapy can be utilized.[24,25] For those who do not respond, minimally invasive treatments like botulinum toxin, corticosteroids, or hyaluronic acid injections may be considered, while surgical options include arthrocentesis and arthroscopy for refractory cases.[26] The key objective is to relieve pain, reduce joint noises, and rehabilitate normal jaw function.[8]

Pharmacotherapy for temporomandibular joint dysfunction syndrome (TMJDS) encompasses various medications in both topical and systemic forms, including NSAIDs, muscle relaxants, opioids, benzodiazepines, sedatives, and antidepressants. This study focuses on comparing two of these medications. NSAIDs are the primary choice for managing inflammatory pain related to TMJDS, but they can have side effects like gastrointestinal issues, prevention of thrombosis, respiratory complications, elevated blood pressure, and nephrotoxicity.[27,28,29]

Muscle relaxants, such as diazepam and baclofen, help reduce pain and muscle spasms by inhibiting motor neuron impulses.[18,31] Benzodiazepines and sedatives can help mitigate emotional stress, providing benefits through central nervous system actions rather than direct muscle relaxation.[29,31] Clinicians should be cognizant of the risks of drowsiness and dependence, advising that benzodiazepines be prescribed for no more than four weeks.[30] Tricyclic antidepressants or anticonvulsants may be considered in patients who do not respond to NSAIDs, benzodiazepines, or muscle relaxants.[30,32]

One trial found that the mean change in pain score was 4.63±0.66 (on 10cm scale) with NSAIDs and mean change in maximal mouth opening was 5.23±1.21 with NSAIDs.[33] With muscle relaxant the mean change in pain score was 45.0±14.9 (on 100mm scale which can be converted as 4.5±1.49 on 10cm scale) with muscle relaxant and mean change in maximal mouth opening was 8.4±1.4mm with muscle relaxant.[34]

This article aims to compare the action of NSAIDS and muscle relaxants in strategies involved in dealing with disorders of TMJ, specifically assessing improvements in average pain and average mouth opening. It references a study evaluating maximum mouth opening and pain scores in patients using Ibuprofen (an NSAID) and diazepam (a muscle relaxant).[19,25] This study improved pharmacological management and paved the way for a comprehensive pharmaceutical approach in managing temporomandibular joint disorders. This study has some major drawbacks that must be mentioned. First, the group's size was limited, which may have impacted on the reliability. Secondly, the sampled population's geographic limitations restrict the results' applicability, therefore these outcomes cannot be applied to other groups with regional and cultural heterogeneity. While NSAIDs are routinely prescribed for TMJ disorders, no trial has explicitly compared NSAIDs and muscle relaxants in this context. The current project seeks to establish a non-invasive treatment option, advocating for the use of oral muscle relaxants for TMJ dysfunction in adults.

METHODOLOGY

Study sample and participants:

This randomized control experiment was undertaken at Riphah International University's Maxillofacial and Oral

Surgery Department in Islamabad, Pakistan. The sample size was determined using the World Health Organization's (WHO) sample size calculator.[35] Sample size of 60 was taken, having 30 in each group. Power of test was kept 90%, participants, the research population was gathered using specified inclusion and exclusion criteria. The inclusion criteria were male and female patients aged 20 to 50 who had been diagnosed with temporomandibular joint (TMJ) problems and were otherwise free of comorbidities. Exclusion criteria were employed to minimize ambiguity in the results. Patients with erupting third molars, active middle ear infections, those diagnosed with primary psychiatric disorders, muscular dystrophy, or facial paralysis, and individuals with systemic joint disorders such as metabolic diseases or rheumatoid arthritis were excluded as well. Patients who had a history of TMJ surgery, maxillofacial trauma, or prior orthodontic treatment were also not included in the study. There were sixty participants in the study. The total population was segregated into two distinct groups, each group comprised of thirty individuals. Both groups received different drugs. Patients in Group A were given 400 mg ibuprofen twice daily. Patients in Group B were given oral diazepam 5mg.Patient demographics, pre-operative and post-operative symptoms, and the extent of pain and jaw mobility were recorded using performas, visual analogue scales, and vernier callipers. Preoperative Orthopantograms of patients were recorded to rule out TMJ pathologies.

Ethical issues

The Permission to collect data and conduct research was approved by the Riphah International University Ethical Committee (Ref No. IIDC/IRC/2022/009/001). Informed written consent was obtained from the patients before the study and all patient personal information was kept confidential. It was conducted within the national and ethical guidelines of the institute.

Outcome variables

The outcome variables in the study were the changes; increase or decrease in extent of pain and mouth opening of temporomandibular joint post treatment with ibuprofen and oral diazepam in middle aged (20-50 years) males and females.

Variable predictors

The efficacy of NSAIDS (ibuprofen 400 mg) and muscle relaxants (oral diazepam 5mg) was compared, by analysing the changes (increase or decrease) in the symptoms; extent of pain and mouth opening of people suffering from temporomandibular joint dysfunction syndrome post treatment.

Other covariates

Apart from drug use, age and gender of the population were considered.

STATISTICAL ANALYSIS

Descriptives

For comparisons of pre-operative vs. post-operative mouth opening, we utilized scatter plots supplemented with KDE density shading to highlight the distribution of data points and trends across the treatment groups. The significance of differences in mouth opening before and after treatment with respective drugs was determined through permutation tests, denoted by an asterisk (*). Similarly, for pre-operative vs. post-operative VAS pain score, we employed KDE-based scatter plots to visualize the changes in pain levels stratified by drug group, with asterisks marking statistically significant differences based on permutation testing. Finally, we visualized the relationships between age and pre-operative/post-operative mouth opening using KDE plots, which provided a clear representation of how age influences mouth opening performance before and after treatment, stratified by oral diazepam and ibuprofen treatment groups. The plots were generated using Python's Seaborn library, which provides comprehensive tools for statistical visualization, and Matplotlib for figure adjustments and presentation clarity.

To evaluate the effects of oral diazepam and Ibuprofen on post-operative improvements in mouth opening (measured in mm) and reductions in VAS (pain) scores, we employed a non-parametric permutation testing approach. This method is particularly well-suited for small sample sizes because it avoids assumptions of normality, making it ideal for our dataset. The rationale behind permutation testing is that by randomly shuffling the group labels (diazepam and ibuprofen), we can generate a null distribution of differences in the test statistic (mean difference between pre- and postoperative scores). We then compare the observed difference to this null distribution to calculate a p-value, which reflects the likelihood of obtaining such a difference by chance.

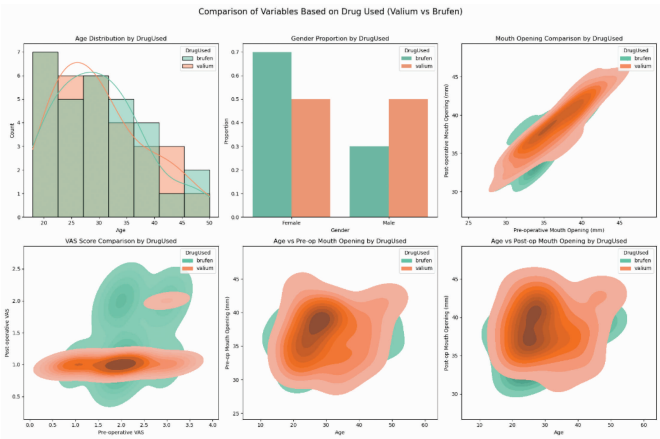
To ensure robustness, we incorporated bootstrapping, a resampling technique that estimates the variability of the observed differences by repeatedly sampling with replacement. This methodological framework enabled a comprehensive investigation of the effects of diazepam and ibuprofen on postoperative outcomes while employing strong statistical tools to ensure validity of the treatment outcomes.

RESULTS

The results from the permutation tests, visualized in the

figure, reveal significant differences in postoperative improvements for diazepam and less pronounced effects for ibuprofen. diazepam and less pronounced effects for ibuprofen. For the month opening, the diazepam demonstrated a statistically significant improvement with a mean difference of approximately 2 mm and a p-value of (p = 0.0301). Patients using oral diazepam (Wilcoxon signed-rank test, p = 0.02) had a significant improvement in postoperative mouth opening compared to those using ibuprofen (p = 0.45). The use of oral diazepam exhibited a substantial decrease in postoperative pain (p = 0.001), compared to patients taking ibuprofen (p = 0.12).

FIGURE 1: Variables characterized by drug use (Figure 1a to 1f, top to bottom, left to right)



This graphic shows a thorough comparison of different patient metrics according to the medication (oral diazepam vs. ibuprofen). Six subplots provide information about how patient characteristics and treatment outcomes are distributed. The plot shows drug use by age distribution of patients; both drugs exhibit peak ranges in the 25–30 years age group. There was no statistically significant difference between drugs used and ages of patients (Mann-Whitney U test, p = 0.38). The plot indicates the use of oral diazepam significantly reduced the VAS pain levels, with a p-value of (p = 0.0000), whereas ibuprofen proved to be less effective (p = 0.0000). The results strongly support that oral diazepam is more effective compared to Ibuprofen in improving postoperative symptoms. Age Distribution by Drug Used: Both oral diazepam and ibuprofen show a similar age distribution with no significant difference, as no asterisk is present. (Figure 1a)

Gender Proportion by Drug Used: The plot shows males were using oral diazepam in higher proportions than females who were taking ibuprofen more frequently. (Figure 1b)

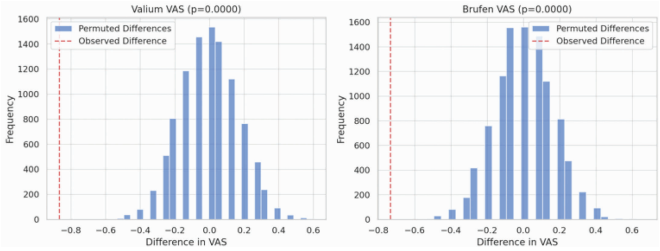
Comparison of Mouth Openings by Drug Type: a bivariate density map comparing the pre- and post-operative mouth openings with the drugs used reveals a significant improvement in mouth opening post-treatment in patients using diazepam, denoted by "*," while ibuprofen did not show significant improvement. (Figure 1c)

Comparison of VAS pain score by drug type: The fourth subplot emphasizes the changes in VAS (pain) scores before and after drug therapy. Use of diazepam exhibited a significant decrease in postoperative pain (p = 0.001). (Figure 1d)

Age and Drug-Related Pre-Op Mouth Opening: The figure shows a contour density plot comparing the pre-operative changes in mouth opening in millimetres for the two drugs, ibuprofen, and diazepam. Two intersecting contour density fields can be seen; the green outlines show patients who took ibuprofen 400mg twice daily, and the orange contours represent patients who used oral diazepam 5mg once daily. The darker areas of each contour correspond to locations with higher density. (Figure 1e)

Age vs. Post-op Mouth Opening: improvements in postoperative jaw mobility seem to be significantly more consistent with oral diazepam. The figure shows a contour density plot comparing the postoperative changes in mouth opening in millimetres for the two drugs, ibuprofen, and oral diazepam. Diazepam exhibited a broader range of postoperative mouth openings. (Figure 1f)

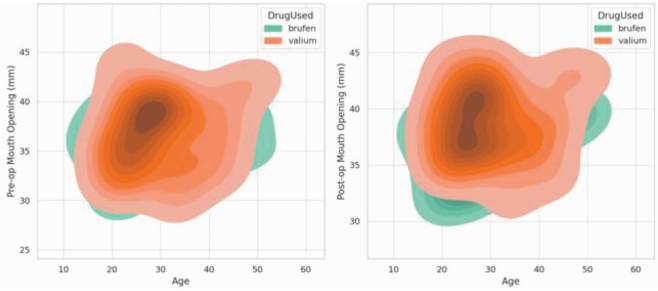
FIGURE 2: Comparison of Oral diazepam and ibuprofen in Visual Analog Scores.



The figure describes the distribution of permuted differences in the Visual Analogue Scale (VAS) scores for the two drugs "Diazepam" (on the left) and "Ibuprofen" (on the right). In the figures, the x axis shows differences in VAS pain score values, while on the y axis frequency is represented. To assess the importance of the stated outcomes, the plot represents the results of a permutation test that compares observed variations in VAS pain score values to a distribution of random permutations. The graph shows that diazepam and ibuprofen both showed a statistically significant effect on the VAS pain score (p = 0.0000). Both treatments have a real effect on the outcome. The permutation tests depict that the observed differences are much different from what would be expected under the null hypothesis. The effect is likely in terms of pain relief and other variables related

to the VAS pain score. The results from the permutation tests, visualized in the figure, reveal significant differences in postoperative improvements for diazepam and less pronounced effects for ibuprofen. For mouth opening, diazepam demonstrated a statistically significant improvement with a mean difference of approximately 2 mm and a p-value of (p = 0.0301), indicating that this observed difference is unlikely due to chance. (Figure 2)

FIGURE 3: Mouth Opening Comparison Between Valium and Brufen



The figure shows two contour density plots that compares the pre-operative and post-operative changes in mouth opening in millimeters for the two drugs, Ibuprofen and diazepam. Each map depicts the distribution of mouth opening as a function of age, using color-coded contour lines.The x-axis represents age (10-60 years), while the y-axis represents pre-operation mouth opening (25-45 mm). You may see two intersecting contour density fields: green outlines depict patients who used ibuprofen 400mg twice daily whereas the orange contours represent patients who took diazepam 5mg. The darker areas of each contour correspond to locations with higher density.

DISCUSSION

The present study highlights the impact of diazepam 5mg and ibuprofen 400 mg by comparing their effectiveness in treating Temporomandibular Joint Dysfunction Syndrome (TMJDS). Patients may complain about limited mouth opening, along with crepitus, clicking, or grating.[14-16] Previous studies conducted on this topic show no evidence of non-steroidal anti-inflammatory drugs preferred over muscle relaxants or vice versa for the resolution of symptoms of pain and trismus in temporomandibular joint disorders. In this research, the efficacy of ibuprofen (NSAIDs) and oral diazepam (benzodiazepine), used in the treatment of TMJDS, is compared. In another trial, patients were randomly allocated to receive one of four treatments: placebo, diazepam, ibuprofen, or an amalgamation of the two. Pain, mood, muscle tenderness, maximum interincisal opening, and plasma levels of â-endorphin were evaluated. Pain decreased substantially in the diazepam and combination groups, as assessed by a visual analogue scale, but ibuprofen and placebo had no meaningful effects.[32,26]

This study revealed that oral diazepam exhibited a substantial decrease in postoperative pain (p = 0.001), compared to patients taking ibuprofen (p = 0.12). The findings outlined in the parent article, conducted in Pakistan, compared muscle relaxants and NSAIDs. It indicates that the average pre-treatment VAS score was recorded at 6.20 ± 1.1. The mean score in Group A was 6.15 ± 1.12, whereas in Group B it was 6.25 ± 1. 00. The difference in pre-treatment VAS pain score between the two groups was not statistically significant.[25]

Comparison of pre- and postoperative mouth opening reveals a significant improvement for patients using oral diazepam. In contrast, ibuprofen did not exhibit a significant improvement in mouth opening. The article for this study gives a maximum mouth opening of 5.23±1.21mm in patients with non-steroidal anti-inflammatory drugs and 8.4±1.4mm in patients with muscle relaxants. Likewise, the post-treatment pain scores are 2.15±1.12 and 3.20±1.04 with non-steroidal anti-inflammatory drugs and muscle relaxants.[25] A study conducted in Italy compared Oral and topical NSAIDs which showed difference between two groups was not significant P value > 0.05 in pain relief as well as insignificant difference in mouth opening between the two groups P value > 0.05. A p value exceeding 0.05 indicated an insignificant difference in mouth opening between the two groups.[34]

Less than 10% of patients do not respond to conventional treatments, including muscle relaxants, analgesics, antirheumatic medications and local procedures. When these techniques do not endeavour, arthroscopy and arthrocentesis can aid with functionality and offer momentary relief. Intra-articular corticosteroid injections have to be constrained to one usage and saved for instances that are challenging to treat temporomandibular joint disorders. Open surgery, including alloplastic joint replacement, may be indicated in extreme cases (less than 1% of cases) where all other options have been tried and failed.[38]

Current research reports the role of ibuprofen and Oral diazepam in treating the symptoms of temporomandibular joint dysfunction syndrome, which is a common pathology in the Pakistani population. This study was a clinical trial aiming to compare the two drugs. Due to the long-lasting nature of TMD, clinicians need proper training and complete awareness of the perils and benefits associated with any medications used for proper intervention. This study improved pharmacological management and paved the way for a comprehensive pharmaceutical approach in managing

temporomandibular joint disorders. This study has some major drawbacks that must be mentioned. First, the group's size was limited, which may have impacted on the reliability. Secondly, the sampled population's geographic limitations restrict the results' applicability, therefore these outcomes cannot be applied to other groups with regional and cultural heterogeneity.

CONCLUSION

The findings prove that oral diazepam significantly reduces postoperative pain and improves mouth opening, as demonstrated by statistically significant data, whereas ibuprofen does not show a noteworthy impact on either postoperative pain levels or improvements in mouth opening, with results lacking statistical significance. Thus, diazepam emerges as the more effective treatment option than ibuprofen in improving both postoperative jaw mobility and pain reduction. As per result the current study proved that oral diazepam had better effects in management of temporomandibular dysfunction syndrome and paves the way for better pharmaceutical management of patients with temporomandibular disorders.

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DATA AVAILABILITY

Data can be provided by the corresponding author on reasonable request.

SAMPLE SIZE CALCULATION

The sample size was determined using the World Health Organization's (WHO) sample size calculator

CONFLICT OF INTEREST

There was no conflict of interest among the authors.

ETHICAL APPROVAL

The study was approved by the ethical board committee of Islamic International Dental Hospital. The study and procedures were performed in accordance with the ethical standards of the institution.
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CLINICAL TRIAL

Not applicable

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AUTHOR CONTRIBUTIONS

- **Zainab Sohail Raja;** conceptualization and design of the study and Sample Size collection. As the lead author, she took a significant role in the overall coordination of the research project.
- **Usama Mushtaq, Haleema Bibi, Uzair Luqman;** gathered and organized data and interpretation of results.
- **Noor Fatima, Syeda Seerat Batool, Hania Noor;** manuscript writing, verification of references and formatting of the article
- **Mahnoor Fatima;** proofreading of the article
- **Javed Ashraf;** Designed the theoretical foundation for the research, Statistical analysis,data interpretation

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