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Effectiveness of Butorphanol Intra Articular Injection in Signs and Symptoms of Internal Disorders of the Temporomandibular Joint Among Yemeni Patients in Sana'a City.

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ABSTRACT

Background and aim: TMJ arthralgia is a painful ailment that is thought to be related to local inflammation in the jaw joint. The purpose of the current study was to evaluate the effectiveness of a single intra-articular (IA) injection of butorphanol into the TMJ for lowering pain and improving mouth opening. The concept was that butorphanol would significantly lessen TMJ pain and improve mouth opening.

Methods: Eleven patients were treated in this serie, which was followed up on for three months. Participants in the study had to be at least 18 years old and have a unilateral TMJ arthralgia diagnosis. Butorphanol IA injections weighing 1 mL were given to all individuals. The main result was an analysis of the per protocol population's change in recorded pain intensity on a visual analogue scale (VAS) at maximum jaw opening.

Results: Mouth opening improved after treatment as values increased: 1 week after treatment mean ± SD = 3.072 ± 0.373, after 1 month of treatment the values of mouth opening increased significantly, the highest values occurred after 3 months of treatment where the mouth-opening values were twice the pre-treatment period. Pre-treatment central trend measures of pain score were: the mean ± SD =7.364 ± 1.12, the pain score decreased after treatment, one week after treatment the mean ± SD =3.636 ± 1.748, one month after treatment values decreased significantly, the lowest pain scores occurred after 3 months of the treatment in which 25% of patients recorded 0 pain and 75% of patients recorded 1 or less pain score.

Conclusion: Following a single-dose IA injection, butorphanol was beneficial for lowering pain and improving mouth opening in individuals with TMJ arthralgia.

CONTENTS

1. Introduction:

Bristol-Myers created butorphanol, a synthetic agonist-antagonist opioid analgesic of the morphinan type[1]. Levorphanol shares the closest structural kinship with butorphanol. The tartrate salt of butorphanol is offered in formulations for injection, tablets, and intranasal spray. The intranasal spray formulation of

butorphanol is most frequently used to treat migraines. Additionally, it can be administered parenterally to treat moderate to severe pain, act as a supplement to a well-balanced general anesthesia, and ease childbirth pain. Additionally, butorphanol works well to lessen post-operative shivering. When it comes to relieving pain, butorphanol works better on women than on males [2]. At the -opioid receptor, butorphanol exhibits partial agonist, antagonist, and partial agonist action (Ki = 2.5 nM; EC50 = 57 nM; Emax = 57%) [2]. When these receptors on neurons in the central nervous system are stimulated, adenylate cyclase is intracellularly inhibited, inflow membrane calcium channels are closed, and membrane potassium channels are opened. As a result, the cell membrane potential becomes hyperpolarized, and ascending pain pathways' action potential transmission is suppressed. Because of its -agonist effect, butorphanol raises cardiac work and pulmonary arterial pressure at analgesic levels. Butorphanol has a lower potential for misuse than other opioid medicines since -agonism can result in dysphoria at therapeutic or supratherapeutic doses.[3]As with other opioid analgesics, central nervous system effects (such as sedation, confusion, and dizziness) are considerations with butorphanol. Nausea and vomiting are common. Less common are the gastrointestinal effects of other opioids (mostly constipation). Another side effect experienced by people taking the medication is increased perspiration [3].

TMJ arthralgia, a painful illness thought to be related to local inflammation, lacks an accompanying systemic inflammatory disease. Common symptoms include pain in the face, jaws, and TMJ that is aggravated by opening and closing the mouth to chew. Occlusal splints, various techniques for sensory stimulation, manipulation of the mandible, and jaw exercises are examples of common active local therapeutic procedures. Non-steroidal anti-inflammatory medications (NSAIDs) and conventional analgesics are frequently administered. The intra-articular (IA) injection of corticosteroids is another well-known treatment that aims to stifle a presumed inflammation if treatment needs to be intensified due to persistent pain [4].

The objective of the present study was to determine the efficacy for reducing pain and enhanced mouth opening of a single-dose intra-articular (IA) injection of butorphanol to the TMJ.

2. Subjects And Methods

The Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Sana'a University Clinics, is the site of the clinical study in the city of Sana'a. Case series study of 11 Yemeni adults carried out in 2023. The study comprised patients with a verified diagnosis of TMJ who were routinely followed up at our clinics.

2.1.Data collection:

Each patient got a clinical evaluation, and all information was gathered on a case sheet with pooled data that was intended for systematic recording. Age, sex, age at illness beginning, and disease duration were considered demographic factors.

2.2.Data analysis:

Epi-Info-Version 7 (CDC) was used for the statistical analysis. Count, percentage, mean, and standard deviation (median and minimum, where necessary) were used to sum up categorical measurements to assess the effectiveness of recent treatment. The cutoff for statistical significance was $p < 0.05$. The 25th percentile is also known as the first quartile (Q1), the 50th percentile as the median or second quartile (Q2), and the 75th percentile as that indicate this value mean is 75% is under this value (less than this value).

2.3.Ethical approval:

The Medical Ethics Committee of the Faculty of Dentistry at Sana'a University provided its official clearance on November 3, 2021, with the reference number 2021-49. Each study participant signed a consent form. All information, including clinical information and patient identification, was kept private.

3. Result

Table 1 shows the outcome of intra-articular injection of butorphanol into the mouth opening of patients with temporomandibular joint disorder at four time periods. Measures of central tendency were presented for each data period include mean ± SD, median, mode, min and maximum mouth opening, and also include the 25th percentile and 75th percentile. Measures of central tendency for the pre-treatment period to open the mouth were as follows: mean ± SD = 2.055 ± 0.353, median = 2.1, mode = 2, minimum to maximum = 2.1–2.8, 25th percentile = 1.8 and the 5th percentile Seventy = 2.2. Mouth opening improved after treatment as values increased: 1 week after treatment mean ± SD = 3.072 ± 0.373, median = 3, mode = 3, minimum to maximum = 2.5–3.8, 25th percentile = 2.9; the value is 75 percentiles = 3.1. After 1 month of treatment the values of mouth opening increased significantly, the highest values occurred after 3 months of treatment where the mouth-opening values were twice the pre-treatment period (Table 1).

Table 1: Outcome of intra-articular injection of butorphanol in the mouth opening of temporomandibular joint disorder patients (n = 11)

Variables	Mouth opening Before treatment	Mouth opening After treatment		
		One week	One month	Three months
Mean	2.055	3.073	3.455	3.982
Standard division	0.353	0.372	0.321	0.098
Standard Error	0.106	0.112	0.097	0.03
Min	1.5	2.5	3	3.9
Max	2.8	3.8	4	4.2
Median	2.1	3	3.5	4
Mode	**2**	**3**	**3.5**	**3.9**
25% ile	1.8	2.9	3.1	3.9
75% ile	2.2	3.1	3.8	4
T-test	19.2	27.4	35.7	134
P value	<0.0001	<0.0001	<0.0001	<0.0001

Pre-treatment central trend measures of pain score were: the mean ± SD =7.364 ± 1.12, median=7, mode=6, min to max=6-9, the 25th percentile = 6 and the 75th percentile =8. The pain score decreased after treatment in which values were decreased. One week after treatment the mean ± SD =3.636 ± 1.748, median=4, mode=4, min to max= 1-7, the 25th percentile = 2 and the 75th percentile =5. One month after treatment previous values decreased significantly, the lowest pain scores occurred after 3 months of the treatment in which 25% of patients recorded 0 pain and 75% of patients recorded 1 or less pain score (Table 2).

Table 2: The result of intra-articular injection of butorphanol in the pain score of patients with temporomandibular joint disorder (n = 11)

Variables	Pain score Before treatment	Pain score After treatment		
		One week	One month	Three months
Mean	7.364	3.636	1.636	0.727
Standard division	1.12	1.748	1.286	0.647
Standard Error	0.338	0.527	0.338	0.195
Min	6	1	0.0	00
Max	9	7	5	2
Median	7	4	1	1
Mode	6	4	1	1
25% ile	6	2	1	0.0
75% ile	8	5	2	1
T-test	21.8	6.9	4.2	3.73
P value	<0.00001	<0.00001	<0.0001	0.0039

4. Discussion

This is the first study conducted in Yemen, to the best of our knowledge and after looking through medical data sets. Acute pain ranging from moderate to severe is treated with butorphanol. The nasal spray version of butorphanol, which is an agonist at kappa receptors but a weak antagonist at receptors, was approved in 1991 after the injection version was approved in 1978. Butorphanol, an injectable medication, has been used in several clinical studies to treat moderate- to severe-level postoperative pain [5]. The mean± SD of mouth opening significantly increased one week after treatment in the current study (3.072 0.373)

compared to the pretreatment period (2.055 ± 0.353), and it also increased significantly one month after treatment, with the highest values occurring after three months of treatment (3.982 ± 0.098) (Table 1). Additionally, pain scores significantly decreased one month after treatment, with the lowest pain scores occurring after three months of treatment, where 25% of patients were included. This finding can be explained by the fact that arthrocentesis performed with enough force can dissolve intraarticular adhesions, removing the source of the joint's negative pressure, eradicating pain, and regaining function by extending mandibular range of motion [6]. Following arthrocentesis, numerous pharmacological substances have been administered into the TMJ space to enhance the procedure's results [7]. Due to their ability to dose-dependently, stereo-selectively, and antagonist-reversibly lower inflammatory severity by 80% in patients who complain of arthritis, κ-opioid medications are regarded as potent anti-inflammatory medications [8]. The fact that pain is typically accompanied by increased activity in primary sensory neurons brought on by intense mechanical or thermal stimuli, or by chemicals released by tissue damage or inflammation, can be used to explain why pain scores were reduced in our study. In the dorsal horn of the spinal cord, primary sensory neurons involved in pain perception primarily produce substance P and glutamate [9]. Numerous clinical research on the use of peripheral opioid analgesia in individuals with chronic articular pain, a highly relevant and common issue, have been conducted. TMJ pain is among these pain disorders one of the most challenging types of articular pain to treat [10]. At 1 week, 1 month, and 3 months in the current trial, the pain score decreased in a highly statistically significant manner. This was in line with the findings of studies by Al-Kibsi et al. [5] and Hassan et al. [11], which found that administering butorphanol at a dose of 1 mg was more effective than tramadol at a dose of 50 mg for postoperative analgesia following the removal of third molar impaction. It was also consistent with the findings of the study by Bhumika et al. [12], which came to the conclusion that efficiency and pain relief were reduced in patients with arthritis by roughly 80% in a dose-dependent, stereo-selective, antagonist-reversible way [8].

The fact that pain is typically linked to increased activity in primary sensory neurons brought on by intense mechanical or thermal stimuli, or by chemicals generated by tissue damage or inflammation, can also be used to explain why the pain score decreased in the current study. In the dorsal horn of the spinal cord, primary sensory neurons involved in pain perception primarily produce substance P and glutamate [9]. Numerous clinical research on the use of peripheral opioid analgesia in individuals with chronic articular pain, a highly relevant and common issue, have been conducted. TMJ pain is among these pain disorders one of the most challenging types of articular pain to treat [10].

When compared to the pre-treatment period, the measurements of mouth opening revealed a statistically significant rise (a very significant increase in mouth opening in the butorphanol treated patients). These symptoms (pain, difficulty opening the mouth) were all related to one another, and the effectiveness of treatment was assessed based on the degree of improvement at the conclusion of care. In symptomatic TMJs, the presence of inflammatory cells and inflammatory mediators, such as arachidonic acid metabolites and cytokines, was shown [13]. The mouth opening was improved by lavage of the superior joint space, which also enlarged the joint gaps and reduced inflammatory cells in the joint [14].

Local activation of κ-opioid receptors has been reported to reduce inflammatory reaction by lowering the levels of interleukin-6 and increasing interleukin-10 without affecting neutrophil migration in a model of periodontal inflammation [17], which may help to explain why butorphanol treatment is superior. Plasma extravasation, a major sign of acute inflammation, is decreased by κ-opioid receptor activation during inflammation in the gut [15]

and the knee joint [16]. The current findings were in line with those of Walker [8], who reported that κ-opioids are potently therapeutic drugs that exert their anti-inflammatory effects through changes in cellular activation and cytokine expression, which reduce adhesion molecule expression, inhibit cell trafficking, reduce the release of tumor necrosis factor, and express and alter mRNA expression and protein levels of substance P and calcitonin gene-related molecules.

5. Conclusion

The results of this case series study led to the following conclusions: butorphanol 1 mg intro-articular is sufficient for managing TMJ symptoms (pain, difficulty opening the mouth wide). With prolonged use and a longer duration of action, it is quite effective. In the clinical research of TMJ ID, butorphanol intra-articular injection following arthrocentesis offers a long-term palliative benefit.

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Conflict of interest

There is no conflict of interest around this work.

Author's contributions

The first author of this study, Taghreed Ahmed M Al-Kibsi, conducted the clinical work and followed up with patients. Second author Hassan A Al-Shamahy assisted with data analysis, drafting and reviewing the paper, and giving final approval to the study.

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