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Cover Page Footnote
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Clinical assessment of intra-articular fentanyl injection following arthrocentesis for management of temporomandibular joint internal derangement

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**A R T I C L E   I N F O**

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1. Introduction

The temporomandibular joint (TMJ) is a unique joint; despite advanced degenerative changes being present in the joint, it allows a range of movement of the associated structures to achieve a modified function [1]. TMJ Internal Derangement (ID) is a common form of temporomandibular disorders (TMDs), almost 80% of adult symptomatic patients with TMD have some form of ID [2].

Data from related literature has suggested that arthrocentesis may be of some benefit to manage symptoms of TMDs. Such a technique was first introduced for the management of sudden onset of closed lock [3]. Arthrocentesis is the single most important non-invasive procedure in musculoskeletal medicine. Therapeutic arthrocentesis is the basic underlying procedure for intra-articular treatment, including; needle lavage and intra-articular injection of therapeutic substances [4].

One of these therapeutic substances is the hyaluronic acid (HA), Exogenous (HA) can stimulate the synthesis of endogenous (HA)—forming synoviocytes of osteoarthritic joints, so reducing joint friction coefficient and decreasing risk of damage [5].

There is scientific and clinical evidence for the analgesic and anti-inflammatory properties of Intra-articular (IA) administered opioids; both in acute and chronic joint pain [6]. Intra-articular injection of opioids has been reported in various studies (Likar et al. [7] 1997; Gupta et al. [8] 2001; Kalso et al. [9] 2002), but according to current study, no survey has been made for the evaluation of fentanyl in TMJ intra-articular injection.

Opioid agonists have powerful anti-inflammatory properties and they exert their action in the periphery via opioids receptors [10].

Fentanyl is a synthetic potent mu opioid receptor agonist characterized by both high potency and high lipid solubility; it is approximately 80 times more potent than morphine and binds strongly to plasma proteins [11,12].

1.1. Review of literature

Temporomandibular joint internal derangement (TMJ ID) is one of the most common forms of TMDs, defined as “an abnormal positional and functional relationship between the articular disk, the mandibular condyle and the articular surfaces of the temporal bone” [13,14].

Pain and limitation of mandibular movements were the main complaint of patients seeking treatment as concluded by Vasconcelos Filho et al. [15] and Wilkes [16].

It is believed that physical action of lysis and lavage in the superior joint space, rather than disc repositioning, is responsible for the success of arthroscopic surgery [17,18]. Arthrocentesis for the TMJ was introduced by Nitzan et al. [19] in 1991 as a minimally invasive safe procedure carries a very low risk, few complications. It appears to have filled the clinical void between failed non-surgical treatment and open arthrotomy [20].

It involves inserting needle inside and washing out the joint with sterile fluids as saline, lactated Ringer’s solution, then fluid in the joint cavity is aspirated with another needle [21,22] and if needed, a therapeutic substance is then injected [23]. This treatment rationale was based on two treatment modalities namely pumping manipulation procedure and the arthroscopic lysis and lavage. Irrigating the superior joint space will result in the creation of the hydraulic pressure and distension, which will release the
drugs into the superior joint space [21,25] and other cells, especially in presence of inervation of opioid receptors in the peripheral nervous system (PNS) that the peripheral analgesic effect of opioids is mediated by activation of viscosupplementation was pioneered in 1982 by Balazs et al. [31]. Viscosupplementation using HA is a procedure that involves injecting HA into a joint to replace the lost HA and potentially stimulate the production of endogenous HA within the joint [32].

It was concluded also that intra-articular injection of tramadol opioid is effective in management of clinical symptoms associated with internal derangements of the TMJ [33]. Opioids exert their pharmacological actions by binding to specific cellular receptors. Receptors are primarily responsible for the observed pharmacological effects. Binding (or blockade) to these receptors alters many clinically important physiological functions, these receptors are widespread throughout the central and peripheral nervous systems [34–36]. These peripheral opioid receptors play a critical role in modulating pain and inflammation. Russell et al. [37] demonstrated that the peripheral analgesic effect of opioids is mediated by activation of opioid receptors in the peripheral nervous system (PNS) and other cells, especially in presence of inflammation. Opioids injected locally into joints produce potent and receptor-specific analgesic effects that are mediated by peripheral opioid receptors, occur in the absence of central analgesic activity, and are naloxone reversible [38]. There is recent evidence of the existence of opioid receptors in synovial tissue [39,40].

Fentanyl, act on the mu receptors, and to a lesser degree on kappa receptors.

In the presence of tissue inflammation; number of nociceptor nerve endings increase and perineural barrier is disrupted, facilitating access of opioid agonists to their receptors, resulting in enhanced peripheral analgesic efficacy of opioids [41,42]. Inflammation as well, increases the permeability of the perineurium, thereby exposing the receptors at the sensory nerve terminals to endogenous and exogenous opioids [42]. Mu-opioid agonists, have therapeutic anti-inflammatory activity by reducing expression of the adhesion molecule, inhibiting cell trafficking, reducing release and expression of tumor necrosis factor (TNF), and altering expression of mRNA and levels of proteins in joint tissue. The mechanism underlying the anti-inflammatory effect of MOR is suggested to be mediated through regulation of cytokine production and T cell proliferation [10].

1.2. Aim of the study

The aim of the current study was to assess intra-articular injection of Fentanyl following arthrocentesis for the management of internal derangement of the tempromandibular joint.

2. Materials and methods

This study was carried out on 40 tempromandibular joints of adult patients suffering from internal derangement. The selected patients were 20 females with age ranging from 20 to 34 years old with mean age about 27 years with chief complain of limited mouth opening, TMJ pain and clicking sounds in the TMJ.

Patients with history of degenerative joint disease or those who had performed previous surgical treatment were excluded from this study; also patients with limited mouth opening caused by only muscle pain or muscle spasm were excluded.

All patients were subjected to:

1. Clinical examination including:
   a. Pain intensity recorded on visual analogue scale (VAS) with endpoints 0 score for no pain and 10 score for the worst pain experienced,
   b. Maximal mouth opening measured inter-incisally with digital calipers,
   c. lateral mandibular excursions mean value of both right and left measures were measured as mean value of both right and left measures
   d. Protrusive mandibular movements measured as the difference in overjet during rest and after protrusion of the mandible.

These parameters were recorded also at the following intervals postoperatively; immediate post-operative, one week, one month and six months after the procedure.

2. Radiographic examination;
   a. TMJ view (open and closed) was taken to detect osseous degeneration
   b. Magnetic resonance imaging for the affected joint had been performed.

Based on these examinations and patient’s history, a diagnosis of TMJ internal derangement was made.

The treated joints were divided randomly into two groups;

1. Group I consisted of 20 joints where arthrocentesis was performed for the affected joints followed by intra-articular injection of 1 ml fentanyl (Fig. 1–3).
2. Group II consisted of 20 joints where arthrocentesis was performed for the affected joints followed by intra-articular injection of 1 ml commercially available sodium hyaluronate.

![Fig. 1. Needles insertion at marked points.](image-url)
3. Results

3.1. Pain score

Descriptive statistics of pain throughout study periods in both groups (Table 1).

Preoperatively and immediately post operative there was no significant difference between Group I and II. In the following post operative observation times 1-week, 1 month and 6 months; there was a significant difference between both groups (p < 0.0001), with higher values recorded in group II.

![A bar chart showing mean values of pain score in both groups.](image)

3.2. Interincisal opening

Descriptive statistics of interincisal opening throughout study periods in both groups (Table 2).

Preoperatively and immediately post operative there was no significant difference between Group I and II. In the following post operative observation times 1-week, 1 month and 6 months; there was a significant difference between both groups, with higher values recorded in group I (p < 0.0001).

![A bar chart showing mean values of mouth opening (mm) in both groups.](image)

3.3. Mandibular functions

![Fig. 2. Tempromandibular joint arthrocentesis.](image)

![Fig. 3. Intra-articular fentanyl injection.](image)

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-operative Mean</th>
<th>Immediate Mean</th>
<th>1 week Mean</th>
<th>1 month Mean</th>
<th>6 months Mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gp I</td>
<td>8.15</td>
<td>6.90</td>
<td>7.60</td>
<td>5.75</td>
<td>4.20</td>
<td>0.547</td>
</tr>
<tr>
<td>Gp II</td>
<td>8.05</td>
<td>6.80</td>
<td>7.57</td>
<td>5.50</td>
<td>4.05</td>
<td>0.142</td>
</tr>
</tbody>
</table>

P.O. = post operatively, Ns = non-significant, *statistically significant at p < 0.05.

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-operative Mean</th>
<th>Immediate Mean</th>
<th>1 week Mean</th>
<th>1 month Mean</th>
<th>6 months Mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gp I</td>
<td>19.90</td>
<td>17.40</td>
<td>16.70</td>
<td>24.00</td>
<td>31.60</td>
<td>0.578</td>
</tr>
<tr>
<td>Gp II</td>
<td>17.20</td>
<td>16.70</td>
<td>15.95</td>
<td>22.45</td>
<td>33.75</td>
<td>0.351</td>
</tr>
</tbody>
</table>

P.O. = post operatively, Ns = non-significant, *statistically significant at p < 0.05.
A bar chart showing mean values of lateral & protrusive mandibular movements.

Preoperatively and immediately post operative there was no significant difference between Group I and II. In the following post operative observation times 1week, 1 month and 6 months; there was a greater mean value in group I.

The results of this study revealed that patients with either disc displacement with reduction or without reduction benefited from the arthrocentesis procedure followed by intra-articular injection of fentanyl and also with intra-articular injection of sodium hyaluronate. Both treatments were able to reduce pain levels, increase maximal mouth openings, lateral and protrusive mandibular movements. However, best results were recorded with arthrocentesis followed by fentanyl intra-articular injection; at 1 week, 1 month and six months intervals; which was superior to arthrocentesis followed by sodium hyaluronate intra-articular injection.

4. Discussion

There are very few studies related to TMJ intra-articular administration of opioids. The current study revealed that fentanyl significantly reduced pain intensity via intra-articular injection through post-operative intervals in comparison with intra-articular sodium hyaluronate injection after TMJ arthrocentesis.

Ever since pain pathways are understood by the clinicians, importance has been given for utilizing the peripheral narcotic receptors for management of pain. Understanding, that opioids can elicit analgesic effects by acting on peripheral opioid receptors, has led to their experimentation in controlled clinical trials [43,44].

Peripheral opioid receptors may be activated only in the presence of tissue inflammation; also, opioid binding sites have been identified in synovial tissues indicating that analgesia is locally mediated. Opioid receptors are mostly located on the terminal end of the nerves and they are activated by inflammation; in this situation afferent ends of the nerves and leukocytes are the target sites. They have a longer analgesic effect in the intra-articular region compared with systemic administration [45–47]. Fentanyl being fat soluble opioid with less histamine release was proved in many studies to be more effective in intra-articular analgesia than morphine [43,48,49]; Histamine is a powerful activator of nociceptors in the local tissues and induces substance-P release. Histamine and substance P produce vasodilatation and increased vascular permeability, which lead to the release of bradykinin. Substance P promotes additional release of histamine from mast cells and serotonin from platelets [50,51]. Fentanyl being fat soluble opioid with less histamine release was proved in many studies to be more effective in intra-articular analgesia than morphine [43,48,49].

In accordance with current study results; Saryazdi et al. [52] found that better postoperative analgesia and less pain score were achieved by fentanyl and pethidine in comparison to deamethasone but the results were not significantly different between fentanyl group and pethidine. Further article by Mandal et al. [49] concluded that although fentanyl is a short-acting narcotic drug, its IA administration provided prolonged postoperative analgesia.

On the other hand; Uysal et al. [53] concluded that a combination of intra-articular morphine and bupivacaine has a longer analgesic duration than a combination of fentanyl and bupivacaine for analgesia after arthroscopic surgery of the knee joint. Furthermore, on contrary to the present study; Manuar et al. [54] suggested that intra-articular ropivacaine gives better postoperative pain relief, with increased time of first analgesic request and decreased need of total postoperative analgesia compared to fentanyl and dexmedetomidine.

The current study revealed that sodium hyaluronate intra-articular injection following TMJ arthrocentesis reduced pain intensity with higher pain score through post-operative intervals than fentanyl intra-articular injection that recorded superior results in decreasing pain intensity.

It is suggested that the analgesic effect of viscosupplementation may occur by blocking receptors and endogenous algic substances in the synovial tissues. A strictly mechanic mechanism by the interruption of trauma caused by mechanic block of the disk or of both adherence zones was also suggested [55], what could explain the effects of therapy in medium and long term, because although the injected HA is kept on the joint only for a few days the results last for months [56,57].

The study results of Yakan et al. [58] were in agreement with the present study as he estimated the efficacy of arthrocentesis and hyaluronic acid injections for the treatment of temporomandibular joint osteoarthritis. Regarding mandibular functions, the present study results showed higher mouth opening values, lateral excursion movements and protrusive mandibular movement records in fentanyl group through different postoperative intervals. In accordance to current study, Hamed T [33]. compared arthrocentesis followed by COX-2 inhibitor versus tramadol in management of internal derangements of the temporomandibular joint. He concluded that intra-articular injection of tramadol which is one of opioids is effective in management of clinical symptoms as he found statistically significant increase in both the maximum mouth opening and the lateral excursion through all periods in COX-2 inhibitor and tramadol groups, as well as significant decrease in mean VAS however, tramadol showed a significant improvement in VSA, maximum mouth opening and lateral excursion superior to those of COX-2 inhibitor group.

5. Conclusion

Finally, it has been concluded that although fentanyl is a short acting opioid drug; its intra-articular injection proved to be able to achieve long term relief of pain as a symptom of TMJ internal derangement, thus it can manage other symptoms as limitation of mouth opening by allowing patients to use their mandibular functions freely without pain. It is worthy to mention that sodium hyaluronate was able to manage TMJ internal derangement symptoms by decreasing pain intensity and increasing mouth opening and lateral excursions; however, fentanyl was superior in achieving significant improvement through post-operative intervals with lower pain scores and higher mandibular functions records.

References
