

## Effect of Glucosamine-Chondroitin Sulfate, Tramadol, and Sodium Hyaluronic Acid on Expression of Cytokine Levels in Internal Derangement of Temporomandibular Joint

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### ABSTRACT

**Aim:** Evaluation of the effect of glucosamine-chondroitin combination, tramadol, and sodium hyaluronic acid in TMJ disorders and its impact on the expression of various cytokines such as IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and PGE2.

**Materials And Methods:** The present study was conducted on 60 patients (males- 30, females- 30) suffering from internal derangement such as disc displacement with reduction of TMJ. The patients were divided into three groups of 20 each. Group I received a combination of 1.5g of glucosamine and 1.2 g of chondroitin sulfate per day and group II received 50 mg tramadol HCL peroral. Group III received Sodium hyaluronate 10 mg/ml, 2 ml injection syringe on each joint. Pain (VAS) scale and maximum mouth opening (MMO) was measured. The level of IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and PGE2 levels were measured using Enzyme-linked immuno sorbent assay (ELISA).

**Results:** There was an improvement in maximum mouth opening in all three groups ( $P < 0.05$ ). There was a reduction in pain in all groups. IL-1 $\beta$ , TNF- $\alpha$ , and PGE2 levels showed reduction while IL-6 showed an increase in value in group II and III.

**Conclusion:** The efficacy of glucosamine chondroitin sulfate, tramadol and hyaluronic acid in TMJ disorders has been found to be effective.

**Clinical significance:** IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and PGE2 levels indicate the risk of TMJ disorders. Thus earlier assessment of

their levels helps in diagnosis, and better management may be done.

**Keywords:** Chondroitin sulfate, Glucosamine, TMJ, Tramadol

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### INTRODUCTION

Temporomandibular joint (TMJ) disorders are increasing in all age groups. It has become the common disorders affecting daily activities such as talking, eating and swallowing, etc. Various etiologies have been postulated causing TMJ disorders. It is considered to be multifactorial. These disorders may be non-inflammatory or inflammatory.<sup>1</sup> Among these, anterior disc displacement with or without reduction and osteoarthritis are common. Precipitating factors such as stress, parafunctional habits, anxiety, and occlusal disharmony are thought to be associated with it. The patient usually encounters pain in joints, limited mouth opening, clicking sound or crepitus while opening and closing mouth, headache and pain in the neck.<sup>2</sup>

Careful assessment of TMJ is necessary to determine disorder. TMJ palpation and muscle evaluation of masseter and sternocleidomastoid (SCM) muscle help in diagnosis. Trigger points on muscles can be elicited by digital palpation.<sup>3</sup>

It has been observed that there is the release of numerous inflammatory mediators such as interleukin 6 (IL-6), interleukin one beta (IL-1 $\beta$ ), tumor necrosis factor-

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alpha (TNF- $\alpha$ ) and prostaglandin E2 (PGE2) levels in joint space. Subsequently, there is a reduction in the secretion of proteoglycans in these disorders. Both glucosamine and chondroitin are proteinaceous, are component of cartilage.<sup>4</sup>

Several modalities such as the use of non-steroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants (TCA), corticosteroids or hyaluronate can help with acute and chronic arthritis pain have been tried. Muscle relaxants and benzodiazepines have been used as conservative treatment modalities. Tramadol is a non-anti-inflammatory drug with central activity. It is narcotic in nature.<sup>5</sup> The present study was conducted to compare the efficacy of the combination of glucosamine chondroitin sulfate, tramadol and sodium hyaluronate in TMJ disorders. It also aimed to evaluate the alteration in the expression of various cytokines such as IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and PGE2.

**MATERIALS AND METHODS**

The present study was conducted on 60 subjects of internal derangement such as disc displacement with reduction of both genders (males- 30, females- 30). The diagnosis was made based on clinical examination and with MRI. All were informed regarding the study, and written consent was obtained. Ethical clearance was obtained from the Institution Ethical Committee prior to the study.

General information such as name, age, gender etc. was recorded. The pain was measured on a VAS scale, and maximum mouth opening (MMO) was measured by calculating interincisal distance. Conscious sedation was performed by injecting (0.1 mg/kg) i.v. midazolam. All were administered auriculotemporal nerve block. Normal saline lavage was performed in upper joint space at a distance of 1 cm anterior to the tragus. This procedure was repeated to get a synovial fluid sample which was stored at -70°C. This sample was used to assess the level of IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and PGE2.

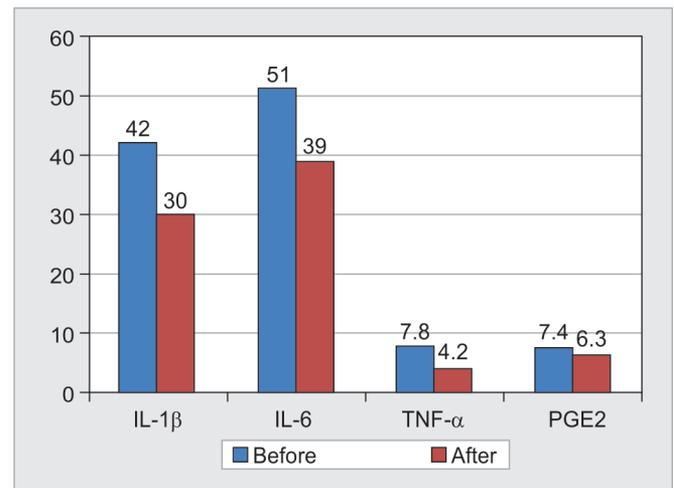
The patients were divided into three groups of 20 each. Group I received a combination of 1.5g of glucosamine and 1.2 g of chondroitin sulfate per day and group II received 50 mg tramadol HCL peroral. Group III received Sodium hyaluronate 10 mg/ml, 2 ml injection syringe on each joint. The same procedure was repeated after 8 weeks to obtain synovial fluid. There was no

control group in the study. The level of IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and PGE2 levels were measured using enzyme-linked immuno sorbent assay (ELISA). Results thus obtained were subjected to statistical analysis using chi-square and Wilcoxon signed rank test. A p-value of less than 0.05 was considered significant.

**RESULTS**

Pain VAS score was 7.12  $\pm$  2.8 before and 3.20  $\pm$  1.5 after treatment in group I. In group II, pain VAS score was 7.28  $\pm$  2.5 before and 3.25  $\pm$  2.2 after treatment. The difference was significant in both groups (p < 0.05). Maximum mouth opening (MMO) was 27.56  $\pm$  4.6 mm and 32.24  $\pm$  5.2 mm before and after treatment in group I whereas it was 26.14  $\pm$  3.8 mm and 30.14  $\pm$  4.4mm before and after treatment in group II. The difference was significant in both groups (p < 0.05). In group III, the pain score was 7.55  $\pm$  3.4 and 3.38  $\pm$  2.7 before and after treatment and MMO was 28.17  $\pm$  3.2 and 31.72  $\pm$  5.1 before and after treatment. The difference was significant (p < 0.05) (Table 1).

In group I, IL- 1  $\beta$  level (pg/mL) was 42 before and 30 after treatment, IL- 6 was 51 and 39 before and after treatment, TNF- $\alpha$  level was 7.8 and 4.2 before and after treatment, and the PGE2 level was 7.4 and 6.3 before and after treatment respectively. The difference was significant except TNF- $\alpha$  and PGE2 level (p> 0.05). (Graph 1)



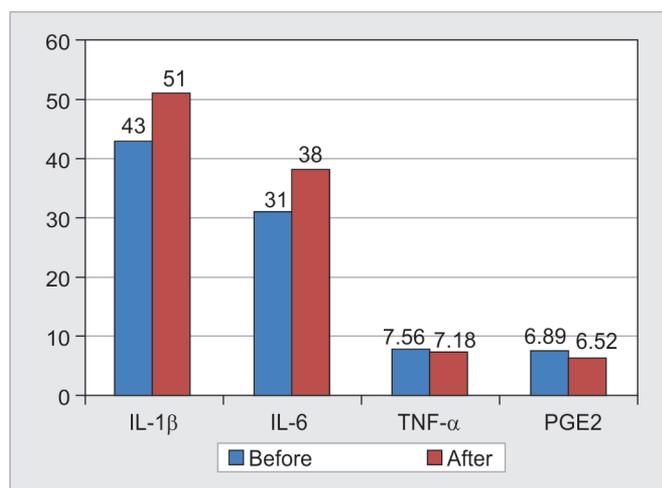
**Graph 1:** Measurement of IL- 1  $\beta$ , IL-6, TNF- $\alpha$  and PGE2 levels in group I

In group II, IL- 1  $\beta$  level (pg/mL) was 43 before and 51 after treatment, IL- 6 was 31 and 38 before and after

**Table 1:** Pain and MMO in both groups

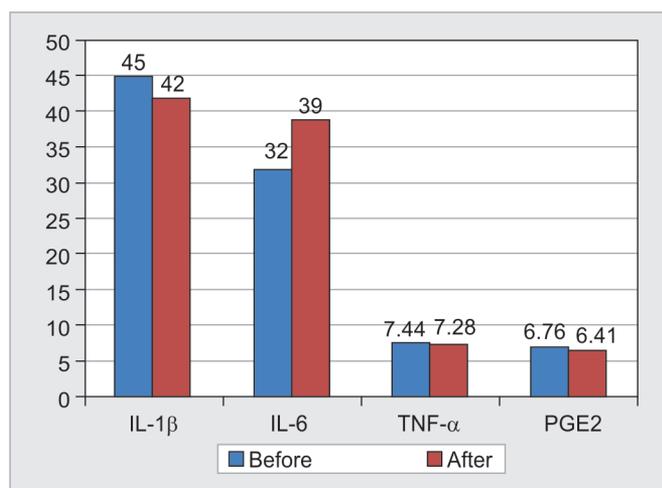
Parameters	Group I			Group II			Group III		
	Before	After	P value	Before	After	P value	Before	After	P value
Pain (VAS)	7.12 $\pm$ 2.8	3.20 $\pm$ 1.5	0.01	7.28 $\pm$ 2.5	3.25 $\pm$ 2.2	0.02	7.55 $\pm$ 3.4	3.38 $\pm$ 2.7	0.01
MMO (mm)	27.56 $\pm$ 4.6	32.24 $\pm$ 5.2	0.05	26.14 $\pm$ 3.8	30.14 $\pm$ 4.4	0.04	28.17 $\pm$ 3.2	31.72 $\pm$ 5.1	0.02

treatment, TNF- level was 7.56 and 7.18 before and after treatment, and the PGE2 level was 6.89 and 6.52 before and after treatment respectively. The difference was non-significant ( $p > 0.05$ ) except IL- 1  $\beta$  level which showed a significant difference ( $p < 0.05$ ). (Graph 2)



**Graph 2:** Measurement of IL- 1  $\beta$ , IL-6, TNF- $\alpha$  and PGE2 levels in group II

In group III, IL- 1  $\beta$  level (pg/mL) was 45 before and 42 after treatment, IL- 6 was 32 and 39 before and after treatment, TNF- level was 7.44 and 7.28 before and after treatment, and the PG E2 level was 6.76 and 6.41 before and after treatment respectively. The difference was non-significant ( $p > 0.05$ ) (Graph 3).



**Graph 3:** Measurement of IL- 1  $\beta$ , IL-6, TNF- $\alpha$  and PGE2 levels in group III

## DISCUSSION

TMJ disorders are evident in the massive scale of the population worldwide. Among inflammatory disorders, internal derangement such as disc displacement with or without reduction is commonly encountered.<sup>6</sup> Disc displacement with reduction is characterized by clicking

sound while opening and closing mouth due to the displacement of a disc. However in disc displacement without reduction cases, there is locking of joint. The condition is so painful that the patient avoids opening the mouth.<sup>7</sup> Excessive mouth opening as in yawning may initiate the pain process. These inflammatory disorders lead to alteration in cytokines levels such as IL- 1  $\beta$  level, IL- 6, TNF- $\alpha$ , and PGE2 level. Chou et al.<sup>8</sup> assessed MMP- 9 and IL- 1  $\beta$  level on the administration of chondroitin and glucosamine sulfate for 25 days. The author found that chondroitin and glucosamine combination significantly decreased IL- 1  $\beta$  level. The MMP-9 level was elevated following administration of chondroitin sulfate. Thus both chondroitin and glucosamine in combination proved to be useful in arthritis.

In the present study, 60 patients diagnosed with internal derangement such as disc displacement with or without reduction were given glucosamine and chondroitin sulfate, tramadol and sodium hyaluronate in group I, II and III respectively. In all patients, arthrocentesis was done with sterile saline, and synovial fluid was obtained. It was observed that pain (VAS) score was reduced significantly in all groups. The decrease was more in group I as compared to group II and group III. There was more reduction in pain score in group I whereas group II and group III had slightly less decrease in VAS score.

Similarly MMO was measured before and after treatment in all groups which revealed that group I had a higher value of mouth opening as compared to other groups. Mouth opening was measured by calculating the distance between the upper and lower incisal edges which was expressed in mm. This is in agreement with Bouloux GF.<sup>9</sup>

In a study by Kaneyama et al.<sup>10</sup> IL- 1 $\beta$ , IL-6, and TNF- levels were measured in synovial fluid of 55 osteoarthritides and five healthy subjects. The measurement of all inflammatory mediators showed higher values in all 55 osteoarthritis patients whereas healthy subjects showed no increase in level.

Hyaluronic acid (HA) is (HMW) a polysaccharide which is a normal component of the joint synovial fluid. Its use in TMJ osteoarthritis has shown improvement in signs and symptoms. The administration of low doses allows prolonging stay in joint space which initiates a therapeutic response.<sup>11</sup> Glucosamine and chondroitin sulfate in the management of TMJ disorders may be useful. Nguyen et al.<sup>12</sup> in their study involved 45 subjects who were given Glucosamine HCL and chondroitin sulfate. There was a decrease in pain value in patients with disc displacement, osteoarthritis, and capsulitis. The author found a reduction in clicking and crepitus

in both TMJ hence advocated the use of these agents in various TMJ anomalies.

The use of tramadol in TMJ disorders has not done so far. We assessed the role of tramadol in relieving pain and increasing mouth opening in patients. The results showed improvement in all factors. Its efficiency is equivalent to morphine. It is useful in both acute and chronic pain. Its use in controlling pain started long back, and for the last four decades it has been the choice of drug for controlling severe painful disorders.<sup>13</sup>

It was observed that IL-1 $\beta$  level (pg/mL) was decreased in group I and III whereas it was slightly increased in group II. Similarly, the level of TNF- $\alpha$  and PGE2 showed a reduction in all groups whereas IL-6 level was increased in group II and III but in group I, the level showed a significant reduction. The increased level of IL-1 $\beta$  and IL-6 in group II is due to poor anti-inflammatory action of tramadol.

Shankland et al.<sup>14</sup> in their study evaluated the role of glucosamine and chondroitin sulfate on osteoarthritis patients and observed that clicking sound and pain was reduced significantly. Quinn and Bazan<sup>15</sup> in their study showed that there is the release of inflammatory mediators such as PGE2 in synovial fluid of TMJ disorders such as internal derangements. In the present study, the PGE2 level was decreased owing to anti-inflammatory role of glucosamine-chondroitin sulfate which causes a reduction in its secretion and thus relieving pain and increasing mouth opening. Glucosamine-chondroitin sulfate has been widely used in TMJ disorders such as arthritis and internal derangement. This combination has shown a reduction in cartilage breakdown. Burch et al.<sup>16</sup> in a group of patients suffering from TMJ disorders compared placebo with tramadol and found that there was the significant reduction in pain on administration of 200mg drug daily.

Gencer et al.<sup>17</sup> assessed the role of hyaluronic acid, tenoxicam, and betamethasone on temporomandibular joint disorders such as disc displacement and osteoarthritis. Intraarticular injection of hyaluronic acid found efficient in controlling pain as compared to tenoxicam and betamethasone. The author concluded that hyaluronic acid is a useful medication for relieving pain and other symptoms in these disorders. Glucosamine chondroitin sulfate, tramadol and hyaluronic acid in TMJ disorders show improvement in mouth opening and reduction in pain values. Joint lavage may be useful in reducing pain in patients.

IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and PGE2 are mediators of inflammation. Their level increases in TMJ disorders such as arthritis, internal derangements, etc. The present study assessed the role of glucosamine chondroitin

sulfate, tramadol and hyaluronic acid on the secretion of these mediators. The limitation of the study is that a small sample size was considered. Drugs such as betamethasone and other corticosteroids were not considered.

## CONCLUSION

The efficacy of glucosamine chondroitin sulfate, tramadol and hyaluronic acid in TMJ disorders has been found effective. There was a reduction in pain and an increase in mouth opening. There was an alteration in inflammatory mediators such as IL-6, IL-1 $\beta$ , TNF- $\alpha$  and PGE2 levels.

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