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OriginalResearch

Evaluating the levels of the biomarkers hs-CRP and IL-6 in patients with temporomandibular disorder treated with LLLT, traditional conservative treatment, and a combination of both.

[1]Altaf HussainChalkoo, [2]Rigzen Wangmo

[1]Professor and Head of Department, Govt Dental College Srinagar, Jammu Kashmir, India

[2]Post Graduate Student, Govt Dental College Srinagar, Jammu Kashmir, India

ABSTRACT:
Temporomandibular disorder are disorders of jaw muscles, temporomandibular joints, and the nerves associated with chronic facial pain. Numerous studies have been conducted over years to determine the ideal biomarkers or set of biomarkers in temporomandibular disorders, tumor necrosis factor (TNF). Interleukin 6 (IL), IL6, IL1 to name a few. The present study was conducted with aim of Evaluating the levels of the biomarkers hs-CRP and IL-6 in patients with temporomandibular disorder treated with LLLT, traditional conservative treatment, and a combination of both. Methods: 18 patients with TMD symptoms randomly assigned to three groups; low level laser therapy only, conservative management and combination therapy. The biomarkers IL6 and hsCRP levels are assessed before the start of therapy and immediately after therapy is concluded. Results:The mean IL-6 (0.55+_0.67) level is less in home-based therapy group at pre-treatment as compared to LLLT only and combination therapy (2.40+-2.49, 3.80+-5.37) respectively. At post treatment the levels are 0.38+-0.48, 1.92+-1.66 and 0.80+-1.24 respectively. The combination group shows greater reduction in IL6 levels as compared to other two groups.There is increase in mean level of hsCRP from 0.38+-0.48 to 1.21+-0.96 and 0.80+-1.24 to 0.91+-1.24 in home based therapy and combination therapy group. While in LLLT only and combination group mean reduction from 1.92+-1.66 to 1.74+-0.89. no statistically significant difference between means levels hsCRP before and after treatment over time. Conclusion: A statistically significant difference in pain intensity VAS post treatment were seen between the LLLT only, home-based and combination therapy group. No significant difference was observed between mean levels of hsCRP and IL-6 before and after treatment.

Keywords: Temporomandibular joint , biomarkers, laser

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Corresponding author: Dr.AltafHussainChalkoo, Professor and Head of Department, Govt Dental College Srinagar, Jammu Kashmir, India

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INTRODUCTION

Temporomandibular disorder (TMD) is a multi-factorial complex process that affects the temporomandibular joint (TMJ) and its associated structures. Its symptoms include facial pain, otalgia, TMJ pain, clicking, crepitus, dental wearing, neck pain, restriction in the mandibular range of motion, and/or headaches.[1]The definition of pain by the "International Association for the Study of Pain" states: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Withdrawal of the painful stimulus usually resolves pain promptly. Sometimes however, pain persists in spite of removal of the stimulus and even after healing of the body. Pain can also arise in the absence of any stimulus, disease or injury. Acute pain is considered to last less than thirty days, while chronic pain is of

more than six months duration or as "pain that extends beyond the expected period of healing". There are three different types of pain; nociceptive, neuropathic and central.[2] The main reason for pain in the orofacial area that does not derive from dental arches is the TMD.[3]

WHAT IS LLLT?

Low-level laser (light) therapy (formerly abbreviated as LLLT) is approaching its 50th anniversary. LLLT was discovered in 1967 by EndreMester at the Semmelweis Medical University in Hungary. Mester was trying to repeat an experiment first conducted by Paul McGuff in Boston USA, who had successfully used the newly discovered ruby laser to cure malignant tumors in rats. However, Mester's custom-made ruby laser possessed only a very small fraction of the power possessed by McGuff's laser. Despite not curing any tumors with his low-power laser beam, he did observe a heightened rate of hair growth and better wound healing in the rats in which he had surgically implanted tumors. This was the first indication that low-level laser light (rather than high power thermal lasers) could have its own beneficial applications in medicine.[4] Almost all LLLT treatments are conducted with red or near-infrared (NIR) light (600–1100 nm), with an output power of 1–1000 mW in a non-heating energy density (0.1–100 J/cm2).[5]

BIOMARKER

In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[6] TMJ inflammatory disorders have a 34.2% prevalence in the population. It can occur due to trauma or an intrinsic and/or extrinsic joint overload that exceeds the adaptive capacity of the joint tissues, generating an inflammation as a consequence. Inflammation is a set of homeostatic phenomena in the vascularized tissues to remove harmful agents and to restore their normal functions. These phenomena are coordinated by the action of inflammation mediators (IM). Histamine, serotonin, kinins, eicosanoids, platelet activating factor, nitric oxide, tumor necrosis factor, and interleukins are among the main IM of TMJ disorders.[7]

AIM

To evaluate the levels of biomarkers hs-CRP and IL_6 in patients with temporomandibular disorder treated with LLLT, traditional conservative treatment, and a combination of both.

MATERIAL AND METHOD

This study was a prospective pilot study conducted in department of oral medicine and radiology, Govt Dental college Srinagar. 18 patients with temporomandibular disorder (both atherogenic and myogenic); 6 patients each randomly assigned to three groups.

Group I: conservative treatment group- application of hot towel, mouth opening exercises, diet and stress counselling

Group II: Low level laser therapy- LLLT at different tender points on muscles for a duration of 60 seconds at each tender points

Group III: combination- LLLT and conservative treatment.

INCLUSION CRITERIA

Patient with TMD following the RDC/TMD criteria
Patient willing to undergo LLLT

EXCLUSION CRITERIA

Patient with recent infection of oro-facial region
Patients with known history of rheumatoid arthritis, SLE and other autoimmune disorder
Patient not willing to undergo laser therapy

METHODOLOGY

The patients from all three groups were evaluated for their serum IL_6 and hs-CRP level prior to any treatment procedure. Following which each group followed different treatment protocol.

Group A: Application of moist hot towel over the tender region twice daily for 20 minutes each followed by jaw exercises.

Group B: Laser therapy Using a (clean-cut laser) GaAs diode laser (Fig 1.a) with wavelength of 980nm, fluency 48J/cm2, power of 0.8W in continuous mode. At each tender points of temporalis, masseter, preauricular, medial pterygoid, lateral pterygoid areas LLLT applied for 60 seconds (fig 1.b).

Group C: combination of both laser and conservative therapy

In both group II and III, 5 sessions of lowlevel laser therapy given for 10 days (0, 2nd, 4th, 6th and 8th day) from a distance of 1cm.

All the subjects were immediately after the last session evaluated for hs-CRP and IL-6.

RESULTS

Fig 1 (a): diode laser (b) application at masseter tender point

(a) (b)

Table 1: Age distribution of study patients in three groups					
Group	**N**	**Mean**	**SD**	**Range**	**P-value**
Group A	6	27.5	12.5	20-45	0.594
Group B	6	23.7	5.9	17-30	
Group C	6	26.5	3.9	20-32	

Table 1 shows the socio-demographic characteristics of the patients participating in this study.
A total of 18 patients were recruited for this study with mean age of 27.5+- 12.5, 23.7+-5.9 and 26.5+-3.9 in group A,Band C respectively.
There were 4 males and 24 females (table 2).
The patients were randomly allocated to three treatment groups: home based therapy (6), LLLT(6), and combination therapy (6). the pre-treatment VAS in three groups is 8.67+-1.03, 8.17+-1.17 and 8.33+-1.03 respectively and shows no statistically significant difference. Post treatment the VAS has reduced to 5.83+-1.47, 2.67+-0.82 and 2.17+-1.17 respectively in each group. Group B and C showed significant reduction in VAS as compared to group A and difference between groups at post treatment is statistically significant ($p<0.001$).

Table 2: Gender distribution of study patients in three groups							
Gender	**Group A**		**Group B**		**Group C**		**P-value**
	No.	**%age**	**No.**	**%age**	**No.**	**%age**	
Male	1	16.7	2	33.3	1	16.7	0.725
Female	5	83.3	4	66.7	5	83.3	
Total	6	100	6	100	6	100	

Table 3: Pre-treatment VAS, IL-6 and hs-CRP in three groups							
Parameter	**Group A**		**Group B**		**Group C**		**P-value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
VAS	8.67	1.03	8.17	1.17	8.33	1.03	0.722
IL-6	0.55	0.67	2.40	2.49	3.80	5.37	0.289
hs-CRP	0.38	0.48	1.92	1.66	0.80	1.24	0.115

Table 4: Post-treatment VAS, IL-6 and hs-CRP in three groups							
Parameter	**Group A**		**Group B**		**Group C**		**P-value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
VAS	5.83	1.47	2.67	0.82	2.17	1.17	<0.001*
IL-6	0.38	0.48	1.92	1.66	0.80	1.24	0.115
hs-CRP	1.21	0.96	1.74	0.89	0.91	1.24	0.399

Table 5: Pearson's correlation analysis between the clinical biomarkers and pain outcomes				
Parameter	**VAS Pre-treatment**		**VAS Post-treatment**	
	r-value	**P-value**	**r-value**	**P-value**
IL-6 Pre-treatment	-0.081	0.728	-0.484	0.042*
IL-6 Post-treatment	0.092	0.715	-0.061	0.812
hs-CRP Pre-treatment	0.367	0.135	-0.203	0.419
hs-CRP Post-treatment	0.137	0.586	-0.195	0.439

The IL6 and hsCRP levels at both pre-treatment and post treatment do not show any statistically significant difference.(Table 3, 4)

Effect of the treatment (LLLT, home based therapy and combined treatment) on Interleukin6 IL6 biomarker:

The mean IL-6 (0.55+_0.67) level is less in home-based therapy group at pre-treatment as compared to LLLT only and combination therapy (2.40+-2.49, 3.80+-5.37) respectively. At post treatment the levels are 0.38+-0.48, 1.92+-1.66 and 0.80+-1.24 respectively. The combination group shows greater reduction in IL6 levels as compared to other two groups.

For the effect of the treatment interval time on IL-6, the results revealed that there was no statistically significance in the difference between the mean levels IL-6 before and after treatment over time.

Effect of the treatment (LLLT, home based therapy and combined treatment) on highly sensitive C reactive protein (hs-CRP) biomarker:

There is increase in mean level of hsCRP from 0.38+-0.48 to 1.21+-0.96 and 0.80+-1.24 to 0.91+-1.24 in home based therapy and combination therapy group . While in LLLT only and combination group mean reduction from 1.92+-1.66 to 1.74+-0.89. no statistically significant difference between means levels hsCRP before and after treatment over time.

Pearson's correlation analysis was performed to determine the association between clinical biomarkers and pain outcomes(table 5)

DISCUSSION

Effects of the treatment (standard therapy, LLLT only and combination therapy) on interleukin 6 (IL-6):

IL6 is a glycopeptide with a molecular weight of 26kDa and produced by fibroblasts, osteoblasts, endothelial cells, monocytes, keratinocytes, T cells and B cells.[3] IL6 has been identified as one of the most important pro-inflammatory cytokines in the etiology of TMJ with internal derangement. Cytokines acts locally and respond mainly to cellular stresses in contrast to hormones. Local stresses to synovial tissues of the TMJ can produce pro-inflammatory cytokines such as IL6 and manifestations such as pain and dysfunction of mandibular movements are seen.[8] In the present study the mean IL-6 (0.55+_0.67) level is less in home based therapy group at pre-treatment as compared to LLLT only and combination therapy (2.40+-2.49, 3.80+-5.37) respectively. At post treatment the levels are 0.38+-0.48, 1.92+-1.66 and 0.80+-1.24 respectively. However, there is reduction of IL6 levels post treatment irrespective of groups. The combination group shows greater reduction in IL6 levels as compared to other two groups. This may be attributed to the action of proinflammatory cytokines that stimulates hypothalamic-pituitary-adrenocortical (HPA) axis by inducing the release of corticotrophin releasing hormone (CRH). stressful occurrences have been linked to increase symptomatology in TMD patients. Costello et al[9] in 2002 reported an association between stress and IL6 in Tmd patients whose level of IL6 reduced after their depressive moods were corrected, as compared to controls. Another study indicating similar results done by Wang et al in 2015, who showed laser therapy in conjunction with aerobic training providing a therapeutic approach for reducing inflammatory markers.

Effects of the treatment (standard therapy, LLLT only and combination therapy) on hsCRP:

CRP is used as one of the markers of choice in monitoring the acute phase response because the markers increase to a relatively high concentration compared to basal concentration.[10] In the dental treatment specificity, the elevated level of CRP has been found in many diseases, such as periodontal disease, gangrenous pulp, fungal diseases of prosthetic base, or posttraumatic conditions—fractures of the jaws.[11] The result of the present study shows that the mean hs-CRP levels increased from 0.80+-1.24 to 0.91+-1.24 post operatively, but were not statistically significant. Yamazaki[12] also presented a similar findings that showed no statistically significant difference in IL6 and hsCRP before and after therapy. The author suggested that the lack of statistical significance may be due to varying contributions of periodontal disease to the total burden of inflammation in different patients. Conclusively, the fact that hsCRP can be changed by any inflammatory activity in the body could be the reason why there are no significant difference.

The result of present study showed no significant correlation between pain intensity and biomarkers level except for IL-6 at baseline and VAS directly after treatment. This result is in accordance to other studies which demonstrated that hs-CRP levels are

normal in TMD patients and the pain intensity is not directly related to inflammation.[10] Lack of statistically significant differences may be due to the fact that biomarkers were analysed from serum and not TMJ fluid and varying contribution of TMDs to the total burden of inflammation in different patients.

CONCLUSION:

A statistically significant difference in pain intensity VAS post treatment were seen between the LLLT only, home-based and combination therapy group. No significant difference was observed between mean levels of hsCRP and IL-6 before and after treatment. Since study is done on small sample size it needs a larger sample size for effective conclusion.

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