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## RESEARCH ARTICLE

## IMPLICATION OF TRICLOSAN AS AN ANTI-CYTOKINE DRUG IN CHRONIC PERIODONTITIS.

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**Abstract**

**Aim:** The present study evaluates the clinical and immunological efficacy of 0.3% of Triclosan gel as a topical drug application system for the treatment of chronic periodontitis patients in terms of plaque index, gingival index, probing depth, clinical attachment levels (clinical parameters) & level of cytokine IL-1  $\beta$  using ELISA.

**Materials & Methods:** A total of 30 patients suffering with chronic periodontitis (20-50 years) were selected & randomly divided equally into two groups to be treated with scaling and root planing (SRP) + 0.3% Triclosan gel (test group) & SRP (Control group) alone. The clinical parameters were assessed at baseline & 30 days, along with the immunological parameters at baseline and 30 days post treatment.

**Results:** Statistically significant reduction in plaque was achieved for both the groups while reduction in gingival index was statistically significant in test group only. When compared to baseline mean pocket probing depth was found to be significantly reduced in test group in comparison to control group. Clinical attachment levels showed statistically significant reduction in both the groups from baseline to 30 days and no significant difference were present in both the groups. Further Test Group demonstrated a statistically significant reduction in level of cytokine IL-1 $\beta$  as compared to Control group from baseline to 30 days.

**Conclusion:** This study, thus demonstrated that 0.3% Triclosan gel can be effectively used as a topical drug delivery system as an adjunct to scaling and root planing for the treatment of in chronic periodontitis patients.

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**Introduction:-**

In 1972, Triclosan was first used in the healthcare industry.<sup>1,2</sup> It is a phenyl-ether, or chlorinated bis-phenol, with a broad-spectrum antimicrobial as well as anti-inflammatory action which is classified as a Class III drug by the FDA (Class III drugs are compounds with high solubility and low permeability).<sup>3</sup> This is a synthetic, anti-inflammatory and works by blocking the active site of the enoyl-acyl carrier protein reductase enzyme (ENR), which is an essential enzyme in fatty acid synthesis in bacteria. By blocking the active site, it inhibits the enzyme, and therefore

prevents the bacteria from synthesizing fatty acid, which is necessary for building cell membranes and for reproducing.<sup>4,5</sup> Since humans do not have this ENR enzyme, Triclosan has long been thought to be fairly harmless to them. It is a very potent anti-inflammatory, and only a small amount is needed for powerful anti-inflammatory action. Triclosan is being used as an antibacterial and bacteriocidal drug in a large number of consumer products worldwide. It is used commercially (e.g. hospitals), in personal hygiene applications such as handwashes, body washes, toothpastes, and mouth rinses, and in fabrics and plastics to inhibit microbial growth. The use of Triclosan for toothpastes and mouthwashes in its maximum concentration is 0.3% and 0.2% respectively. The primary aim of this randomized, controlled clinical trial was to measure and document the *in vivo* local anti-inflammatory (IL-1  $\square$  level) effects of topical Triclosan in humans with chronic periodontitis.

### Materials and methods:-

A case controlled clinical, *in-vivo* & *vitro* study for the evaluation of efficacy of 0.3% Triclosan gel in adjunct to scaling and root planing (SRP) in comparison to SRP alone was carried out in correlation with level of cytokine IL 1- $\beta$  in gingival crevicular blood (GC blood) for the treatment of chronic periodontitis. The study was conducted in the Department of Periodontics, Babu Banarasi Das College of Dental Sciences, Lucknow, Uttar Pradesh in collaboration with Department Of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Inclusion criteria: Indian adults of both genders of age range between 20-50 years, Volunteers with diagnosed cases of Generalized Chronic Periodontitis, having a minimum of 20 natural teeth with Probing Pocket Depth (PPD)  $\geq$  5 mm and Clinical Attachment Level (CAL)  $\geq$  4 mm at a minimum of one site in more than 8 teeth, Volunteers should be systemically healthy. Exclusion criteria: Smokers, tobacco and/ or pan masala chewers, alcoholics, drug addicts, Pregnant and lactating females, Persons having systemic diseases or conditions that influence the progression and/or clinical characteristics of periodontal disease, Persons having taken antibiotics and anti-inflammatory drugs within the preceding 3 months or currently taking medications, Periodontal treatment within last 6 months. This study was approved by institutional ethical committee of the Babu Banarasi Das University. The study protocol was explained to all the volunteers and those who accepted were enrolled and grouped into the following categories:

**Group A:** (Test Group) 15 Generalized Chronic Periodontitis subjects treated with scaling-root planing and local application of 0.3% Triclosan gel for 21 days.<sup>6,7</sup>

**Group B:** (Control Group) 15 Generalized Chronic Periodontitis subjects treated with scaling and root planing alone.

### Clinical parameters:-

The following clinical parameters were recorded to the nearest mm with the help of a probe by a single investigator before phase I therapy (baseline) and post-intervention after 30 days at 4 sites per tooth (mesiobuccal, midbuccal, distobuccal, midlingual / midpalatal). Plaque index<sup>8</sup>, Gingival index<sup>9</sup>, Probing pocket depth (PPD), Clinical attachment level (CAL) were measured. A detailed case history recorded and a duly informed written consent of each patient was taken for the purpose of the study.

GC blood samples were collected from 4 sites with deepest periodontal pockets from each volunteer.<sup>10,11</sup> G C blood sample was collected by gently inserting periodontal probe (UNC-15) into the orifice of the periodontal pocket until a slight resistance was felt and then left there for 30 seconds and collected in micro-capillary tubes. Following micro-centrifuge tube, the serum samples were kept on ice, maintaining the temperature 0-4<sup>0</sup> C for the cytokine detection.<sup>12</sup>

**Formulation of Triclosan gel:** The powdered form of Triclosan was provided by DEV IMPEX CHEMICALS, Ahmadabad, Gujarat. Formulation of Triclosan gel was performed by department of pharmacology, college of pharmacy, BBD University, Lucknow. Accurately weighed carbopol 940(2gm) was dispersed in 50 ml of water and kept for 1 hr. The Triclosan powder (0.3gm) was dissolved in 1ml of ethanol and added to above dispersion. 5gm of glycerine, 1 gm calcium carbonate and 0.8 gm sodium luryl sulphate mixed in 5ml of water was added to polymer drug translucent solution. The p<sup>H</sup> of paste was adjusted to 7.0 with the help of tri-ethanolamine to form gel. The weight of final paste was adjusted to 100gm with help of distilled water. The formulation of gel has been done

without use of preservative so that it may not influence the property if Triclosan. The Triclosan gel was made without use of preservative so has been used within 30 days.

**Periodontal treatment procedure:-** Phase I therapy provided to test and control group. Test group subjects were given adjunctive chemical plaque control, in the form of 0.3% TRICLOSAN GEL and were trained regarding it and instructed to apply with finger twice daily, for 21 days. Patients were advised to keep the gel for 60 seconds and not to consume eatables at least for 20 minutes. After 30 days of post treatment, all the endpoints were repeated for clinical outcome and GC blood of the subjects. These samples were again subjected to analysis.

#### Cytokine estimation in gc blood:-

ELISA kits for cytokine by DIACLONE were used for quantification of the levels of cytokine (IL-1 $\beta$ ) in both the groups. Immunoassays for the quantification of the level of selected pro-inflammatory cytokine were carried out as per the protocol provided by the manufacturer.<sup>13, 14</sup>

#### Results:-

**Table 1:-** Comparison (p value) of mean Plaque Index (score) between Group A and Group B.

	Group A	Group B	p-value <sup>1</sup>
Baseline(Group A vs Group B)	2.16 $\pm$ 0.417	2.12 $\pm$ 0.220	0.156
30 days (Group A vs Group B)	0.9 $\pm$ 0.130	1.52 $\pm$ 0.318	0.001*
Group A- Baseline vs 30 days <sup>2</sup>			0.006*
Group B- Baseline vs 30 days <sup>2</sup>			0.019*

<sup>1</sup>Wilcoxon rank sum test, <sup>2</sup>student t-test, \*Significant

A statistically significant reduction (p=0.001) in mean plaque index is seen in Group A (0.9 $\pm$ 0.130) when compared to Group B (1.52 $\pm$ 0.318) at 30 day. Decrease in the plaque index in Group A from baseline (2.16 $\pm$ 0.417) to 30 days (0.9 $\pm$ 0.130) is observed (p<0.05) which was statistically highly significant. Similarly a significant decrease is observed (p=0.019) in Group B from baseline (2.12 $\pm$ 0.220) to 30 days (1.52 $\pm$ 0.318).

**Table 2:-** Comparison (p value) of mean Gingival Index (score) between Group A and Group B.

	Group A	Group B	p-value <sup>1</sup>
Baseline (Group A vs Group B)	2.28 $\pm$ 0.38	2.07 $\pm$ 0.133	0.11
30 days (Group A vs Group B)	0.10 $\pm$ 0.19	0.55 $\pm$ 0.280	0.001*
Group A- Baseline vs 30 days <sup>2</sup>			0.001*
Group B- Baseline vs 30 days <sup>2</sup>			0.478

<sup>1</sup>Wilcoxon rank sum test, <sup>2</sup>student t-test, \*Significant

The mean Gingival Index was significantly (p<0.05) lower among the patients of Group A than Group B at 30 days. Decrease in the gingival index in Group A from baseline (2.28 $\pm$ 0.38) to 30 days (0.10 $\pm$ 0.19) is observed (p<0.05). In contrast; a non significant result observed (p=0.478) in Group B from baseline (2.07 $\pm$ 0.133) to 30 days (0.55 $\pm$ 0.280).

**Table 3:-** Comparison (p value) of mean Probing Pocket Depth between Group A and Group B.

	Group A	Group B	p-value <sup>1</sup>
Baseline(Group A vs Group B)	6.18 $\pm$ 0.352	6.67 $\pm$ 0.291	0.09
30 days (Group A vs Group B)	3.89 $\pm$ 0.772	5.30 $\pm$ 0.273	0.001*
Group A- Baseline vs 30 days <sup>2</sup>			0.006*
Group B- Baseline vs 30 days <sup>2</sup>			0.030*

<sup>1</sup>Wilcoxon rank sum test, <sup>2</sup>student t-test, \*Significant

Statistical results showed that there was a significant difference (p=0.001) in probing pocket depth among the patients of Group A (3.89 $\pm$ 0.772) than Group B (5.30 $\pm$ 0.273) after 30 days. A statistically highly significant decrease was seen in the PPD from baseline to 30 days in Group A (p=0.006). statistically significant decrease was also observed in Group B (P<0.05).

**Table 4:-** Comparison (p value) of mean CAL between Group A and Group B.

	Group A	Group B	p-value <sup>1</sup>
Baseline(Group A vs Group B)	6.24 $\pm$ 2.579	5.70 $\pm$ 3.640	0.997
30 days (Group A vs Group B)	3.64 $\pm$ 1.978	4.35 $\pm$ 2.799	0.443
Group A- Baseline vs 30 days <sup>2</sup>			0.002*
Group B- Baseline vs 30 days <sup>2</sup>			0.002*

<sup>1</sup>Wilcoxon rank sum test, <sup>2</sup>student t-test, \*Significant

The difference between means of Clinical attachment level was non significant ( $p=0.997$ ) among the patients of Group A ( $6.24\pm 2.579$ ) and Group B ( $5.70\pm 3.640$ ) at baseline as well as after 30 days ( $p=0.443$ ). While there was a significant difference has been observed in individual groups; that is  $p=0.002$ .

**Table 5:-** Comparison (p value) of mean level of cytokine (IL- $\alpha$   $\alpha$   $\alpha$   $\alpha$  between Group A and Group B

	Group A	Group B	p-value <sup>1</sup>
Baseline (Group A vs Group B)	1.32 $\pm$ 1.463	0.930 $\pm$ .343	0.91
30 days (Group A vs Group B)	0.21 $\pm$ .324	0.674 $\pm$ .426	0.006*
Group A- Baseline vs 30 days <sup>2</sup>			0.001*
Group B- Baseline vs 30 days <sup>2</sup>			0.063

<sup>1</sup>Wilcoxon rank sum test, <sup>2</sup>student t-test, \*Significant

There was statistically a significant difference in the level (pg/ml) of GC blood /IL-1 $\beta$  while comparing among the patients of Group A and Group B from baseline to 30 days ( $p=0.001$ ). It has been observed that there is significant decrease in Group A from baseline to 30 days, that is ( $p=0.001$ ) while no significant reduction seen in Group B ( $p=0.063$ ).

## Discussion:-

### Clinical parameters:-

The clinical parameters for Plaque index (PI), Gingival index (GI), Pocket probing depth (PPD) & Clinical attachment level (CAL) were assessed & compared at baseline & 30 days.

Plaque index (PI) for both the groups showed statistically significant reduction from 0 to 30 days. The mean plaque index was decreased to ( $0.90\pm 0.10$ mm) 41.66% at 30 days from baseline ( $2.16\pm 0.417$ ) and mean gingival index decreased to  $0.10\pm 0.19$  mm (95.7%) at 30 days from baseline ( $2.28\pm 0.38$ ) which was statistically highly significant in Group A. The significant reduction in PI (plaque index) and GI (gingival index) in Group A was in accordance with the studies done by Virginia Monsul Barnes, Rose Richter et al, (2010). They have conducted a clinical trial to compare the impact of 0.3% Triclosan/2.0% polyvinylmethyl ether maleic acid copolymer for anti-plaque and anti-inflammatory effects with 0.454% stannous fluoride (SnF<sub>2</sub>). They found that Triclosan significantly inhibits de-novo plaque formation and reduces gingival inflammation in comparison to SnF<sub>2</sub>.<sup>15</sup> In another study by Muller HP et al (2006) contrast result was seen, they have evaluated efficacy of 0.3% Triclosan for 10 weeks and found that there is no effect of Triclosan on plaque level.<sup>16</sup> Mankodi, *et al.*, (2011) did a study to evaluate anti gingivitis effect of Triclosan and found similar results that gingival inflammation reduced by 60% in comparison to placebo.<sup>17</sup>

Statistically significant reduction in plaque index was observed in Group B ( $1.52\pm 0.318$  mm) 28.31% at 30 days from baseline ( $2.12\pm 0.220$ ). This result was in agreement with the study conducted by Tunkel, J. Et al (2002), who described that there is significant reduction found in plaque index after scaling and root planing.<sup>18</sup>

The difference in PI & GI between Group A & B from baseline to 30 days was statistically significant ( $p=0.001$ ). A study conducted by Furuichi Y, Ramberg P et al, (1997), who evaluated short-term effect of Triclosan gel locally applied supra-gingivally twice daily for the following 2 weeks. No significant differences were observed between the 2 regimens [(SRP+TRICLOSAN GEL) & (SRP)] regimen regarding plaque scores but the reduction in gingival index scores was significantly greater in the test (SRP+TRICLOSAN GEL) than in the control (SRP) regimen.<sup>19</sup>

The mean gingival index was decreased to ( $0.55\pm 0.280$  mm) (26.57%) at 30 days from baseline ( $2.07\pm 0.133$  mm) in Group B, which was statistically insignificant. Similar results were seen in a study done by Ludovico Sbordone et al, (1990) in which they observed recolonization of the subgingival microflora after scaling and root planing in human periodontitis. They have also revealed that there was no significant change in gingival index at 7, 21 and 60 days.<sup>20</sup>

The mean pocket probing depth (PPD) decreased to 38% from baseline ( $6.18\pm 0.352$ ) to ( $3.89\pm 0.772$ ) 30 days in Group A which was statistically highly significant ( $p=0.006$ ) and gain in mean clinical attachment level (CAL) from baseline ( $6.24\pm 2.579$ ) to 30 days [ $3.64\pm 1.97$  mm (41.67%)] seen after the treatment was statistically significant in Group A. The decrease in probing pocket depth and gain in CAL was significant in present study which was in concurrence to the study done by Cullinan MP et al (2003); they did a double-blind, controlled clinical trial which showed significant decrease in probing pocket depth with use of unsupervised Triclosan /copolymer dentifrice.<sup>21</sup>

In Group B there was also statistical significance reduction to  $(6.67 \pm 0.291)$  20.5% at 30 days from baseline  $(5.30 \pm 0.273)$  in terms of PPD. Ryan ME et al (2005) found similar results that SRP leads to reductions in probing depth. They evaluated that a mean reduction of 1.29 mm for 4-6 mm pockets and a mean of 2.16 mm for pockets of  $> 7$  mm has occurred after SRP.<sup>22</sup>

There was statistically significant difference found in probing depth reduction while comparing in Group A & B ( $p=0.001$ ). Alike results were found in study done by Furuichi Y et al (1999). They compared two groups; (TRICLOSAN+SRP) & (SRP), there was reduction seen in the mean PPD and gain in clinical attachment loss in both the groups. The reduction in PPD was more significant in (TRICLOSAN+SRP) than (SRP).<sup>19</sup> Similar results were observed in this study ( $p<0.01$ ) in terms of gain in clinical attachment loss for Group B which showed significant results from baseline  $(5.70 \pm 3.640)$  to  $[4.35 \pm 2.79 \text{ mm (23.69\%)]}$  30 days from baseline.<sup>19</sup>

There was no statistical significant difference in both the groups from baseline to 30 days ( $p=0.443$ ). Accord results were seen in a study conducted by Arthur J. Bonito et al (2005) in which they found insignificant difference between SRP alone in comparison to SRP in adjunct with Triclosan.<sup>23</sup>

### **Cytokines:-**

Gingival crevicular blood samples were analyzed for specific inflammatory biomarkers using immunoassay and enzyme-linked immunosorbent assay (ELISA) methods which are previously described.

Group A showed statistically significant reduction ( $p=0.001$ ) in the level of IL-1 $\beta$  from baseline  $(1.32 \pm 1.463)$  to 30 days  $(0.21 \pm 0.324)$ . The result of the present study is in accordance with a previous study done by Sheppard A. McKenzie IV (2008).<sup>24</sup> They have evaluated the local pharmacodynamic effects of Triclosan dentifrice on GCF concentrations of inflammatory mediators in subjects with moderate plaque-induced gingivitis and reported that IL-1 $\beta$  levels were significantly suppressed in the Triclosan group; in comparison to placebo group from baseline to 29 days. In the same study a statistically significant suppression ( $p=0.0042$ ) of IL-1 $\beta$  at 2 hours post Triclosan application was observed in the test group.

The result of our study shows agreement with the study conducted by Barros SP et al (2010), who reported that Triclosan significantly down-regulated the expression of Toll-like receptor signalling molecules and IL-1 $\beta$ . Contrast results were seen in study done by Sköld-Larsson K, Yucel-Lindberg T (2003), who evaluated the effect of a Triclosan-containing (0.3%) dental gel on inflammatory mediators in gingival crevicular fluid (GCF), on individuals undergoing orthodontic treatment with fixed appliances. They concluded neither the experimental (Triclosan group) nor the placebo gel applications caused any statistically significant alterations in the inflammatory mediator IL-1 $\beta$ , compared from baseline to 6 weeks.<sup>26</sup>

In our study Group B exhibited statistically non significant decrease ( $p=0.063$ ) for IL -1  $\beta$  level from baseline  $(0.930 \pm 0.343)$  to 30 days  $(0.674 \pm 0.426)$ . Similar results were seen in study conducted by Yoshinari N, Kawase H (2004) to evaluate the relationship between the clinical parameters after non-surgical periodontal therapy and interleukin- 1 $\beta$  (IL-1 $\beta$ ) level in gingival crevicular fluid in patients with chronic periodontitis.<sup>27</sup> They have concluded that there was no effect observed in level of IL- 1 $\beta$  in GCF after SRP. Contrast results were found in terms of IL-1 $\beta$  after SRP in a study done by Konopka L, Pietrzak A, (2012) who found significant decrease in the amounts of IL-1 $\beta$  in comparison from baseline to 4 week after scaling and root planing ( $p < 0.001$ ).<sup>28</sup>

There was statistically a significant difference in the level (pg/ml) of GC blood /IL-1 $\beta$  while comparing among the patients of Group A and Group B from baseline to 30 days ( $p=0.006$ ).

### **Conclusion:-**

The findings of the our study suggested that 0.3% Triclosan gel applied locally (supra-gingival and gingival massage) as an adjunct with scaling and root planing in the chronic periodontitis patients, resulted in significant reduction in level of inflammatory cytokine IL-1  $\beta$ . Therefore it proves to be a better approach for the healing and anti-inflammatory action within periodontal tissues in patients with chronic periodontitis because it does not require the additional visit of patient and bone loss due to surgical procedure can be avoided up to an extent (if periodontal status remains stable). However, further longitudinal studies with larger sample size are required to evaluate the clinical efficacy of Triclosan gel as an adjunct to scaling and root planing in chronic periodontitis patients.



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