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Original Article

Localized Drug Delivery Using Linezolid Hydrogel for Periodontal Therapy

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Abstract

This study aimed to develop a linezolid-based hydrogel and evaluate its performance as a locally administered medication for treating stage II grade A periodontitis. A biocompatibility test was performed using the MTT assay, and hemolysis assays were conducted at different concentrations (2%, 4%, 6%, 8%, and 10%). This treatment trial included 40 individuals with stage II grade A periodontitis. They divided the participants into two groups. Scaling and root planing (SRP) was the only treatment given to group A (control), while linezolid gel and SRP were given to group B (test). Plaque index (PI), gingival index (GI), probing pocket depth (PPD), and clinical attachment level (CAL) were among the clinical data that were documented both at baseline and three months later. According to in vitro analysis, the hemolysis ratio was less than 1% at 2% concentration, and the biocompatibility assay showed 98% cell viability after 94 hours. In vivo analysis was performed using a hydrogel based on 2% linezolid. All clinical measures (PI, GI, PPD, and CAL) showed statistically significant differences ($P < 0.05$) between baseline and three months when compared within groups. In addition, a significant difference favoring group B was observed in all metrics on the inter-group comparison ($P < 0.05$). As a supplement to SRP, locally applied linezolid gel appears to be beneficial for patients with stage II grade A periodontitis.

Key words: Antimicrobial, Hydrogel, Local drug delivery, Periodontitis, Scaling and root planing

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Introduction

The chronic inflammatory multifactorial illness known as periodontitis erodes the tissues that support teeth. Bacteria play a significant part in the onset of disease, even though different aetiologies influence how the disease progresses. Dysbiosis of the microbiota and compromised host defenses cause periodontitis to start and worsen [1]. The genera Streptococci, Capnocytophaga, Corynebacterium, Actinomyces, and Veillonella are examples of oral commensals found in a healthy

periodontium [2, 3]. The growth of subgingival pathobionts, which causes microbiota dysbiosis, is facilitated by oral commensals. During the microbiota's shift from a healthy to a pathogenic state, commensals interact with late-arriving pathobionts in several ways that affect their virulence factor expression, colonization, and accumulation [4]. Important pathobionts that are intimately linked to subgingival plaque in a sick state are *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, and *Fusobacterium nucleatum* [5]. The metabolic activities of pathobionts, which are also essential in host-microbe interactions, are primarily responsible for their pathogenicity. The host cells and tissues are harmed by these bacteria metabolites [6].

In an attempt to lower the bacterial load and change the environmental characteristics of these microbial habitats, mechanical debridement of the afflicted root surface is frequently used as a treatment for periodontitis. According to Winkel *et al*. antimicrobial therapy would enhance the clinical result and perhaps be necessary for a successful course of treatment when used in conjunction with mechanical debridement [7]. Since then, local administration of several antibiotics has been used to treat periodontitis [8-10].

Linezolid is a member of the new class of antibiotics known as oxazolidinones, which are used to treat infections brought on by aerobes and anaerobes that are susceptible to other classes of medications [11]. To stop protein synthesis, linezolid interacts with the 50S ribosomal subunit. It inhibits the formation of biofilms, has excellent pharmacokinetic and pharmacodynamic properties, and has excellent oral absorption [12].

In addition to mechanical debridement, researchers have shown that systemic medication distribution enhanced the rate of tolerance. To achieve a therapeutic impact, excessive dosages were frequently administered or administered repeatedly, which led to detrimental side effects, including systemic toxicity [13, 14]. In contrast to the systemic strategy, controlled local distribution of the antibacterial and anti-inflammatory medications has been demonstrated to be more effective at preserving the drug concentration in the periodontal pocket [15]. Additionally, a variety of techniques, including oral irrigation, fibers, vesicles, strips, gels, and microparticulate systems, are used in controlled local drug administration [16-18]. The hydrogel delivery method is one of them that may control the release of different therapeutic substances, such as cells, macromolecular drugs, and small-molecule medications [19, 20]. Over time and at various locations, these hydrogels can regulate the amount of medication that is supplied to cells and tissues [21].

Numerous hydrogels have been employed in the literature as a supplement to SRP. Hydrogels have been shown in experiments to have the ability to release drugs in a regulated manner [22] and to promote the healing of periodontal wounds [23]. Additionally, hydrogels are a successful local drug delivery method for the treatment of periodontitis [24]. This study's objective was to create a hydrogel based on linezolid and assess how well it works as a locally administered medication for treating stage II grade A periodontitis.

Materials and Methods

Linezolid hydrogel preparation

Sodium alginate solution (2%, w/v) and hyaluronic acid solution (2%, w/v) were prepared by adding 2 gm sodium alginate and 2 gm hyaluronic acid in 100 ml deionized water at room temperature separately. A hydrogel solution was prepared adding both sodium alginate solution and hyaluronic acid solution at 2:1 ratio respectively. Using a magnetic stirrer, a uniform mixture was obtained after 2 hours of stirring. Then 0.2% w/v of linezolid was added into that mixture and kept in the stirrer for another 30 mins. Further linezolid hydrogel was ion-cross linked in 200 mM calcium chloride for 24 hours. Then, the linezolid hydrogel was taken to further experiments.

In vitro analysis

Hemolysis assay

4 ml of fresh anticoagulant (EDTA) whole blood was diluted with 5 milliliters of 0.9 weight percent NaCl solution to create the diluted whole blood solution. The 50µL sample was added into 950µL of 1x PBS solution in a 1.5ml Eppendorf centrifuge tube and incubated at 37 °C for 30 mins. Further 0.2 mL diluted whole blood was added and incubated at 37 °C for 1 h. The solution was centrifuged at 1000 rpm for 10 mins, and after that, a UV spectrophotometer was used to test the supernatant's

absorbance at 545 nm.

Biocompatibility assay

The biocompatibility of linezolid hydrogel along with control (placebo gel) treated on human periodontal ligament tissue-derived primary cells (fibroblasts) was determined over 24 hours by MTT assay. Linezolid hydrogel in different percentages incubated on fibroblast cells was seeded in 96 well culture plates for 24 hours. To determine percent cell viability, the post-incubated cells were replaced with 10 μl of stock MTT dye (10 mg/ml), which was added to each well culture plate and incubated at 37 °C for 4 hours. To dissolve the formazan crystals, the medium was replaced with 100 µl dimethyl sulfoxide in each well, and absorbance was recorded at 570 nm with the Synergy Hybrid Multi-Mode Reader (BioTek, Winooski, VT, US).

In vivo analysis

Patient selection

Forty outpatients from the Department of Periodontology, Saveetha Dental College and Hospitals, Chennai were selected for this study. Patients of both genders of age between 25 to 55 years diagnosed with stage II grade A periodontitis and the presence of at least 20 natural teeth were considered for this study. Patients under antimicrobial or antibiotic drugs for the past 3 months, systemically compromised, pregnant women, lactating mothers, and smokers were excluded from this study.

Study protocol

The study protocol was approved by the Institutional Review and Ethical Committee of Saveetha Dental College and Hospitals, Chennai, India before commencing this investigation (Reference number: IHEC/SDC/PERIO-2204/23/327). Also, every individual involved in the research gave their informed consent. G Power software, version 3.1.9.4 was used to determine the sample size which came out to be 40 (power at 80% and alpha error at 95% confidence level) by considering the mean and standard deviation values from the earlier research [25].

This clinical study was performed to evaluate the efficacy of linezolid hydrogel as local drug delivery as an adjunct to scaling and root planing (SRP) in the management of stage II grade A periodontitis. 20 patients were subjected to SRP alone (group A: Control) and the remaining 20 patients were subjected to SRP + linezolid hydrogel (group B: Test).

Clinical parameters

The clinical parameters recorded were 1. plaque index (PI) (Silness and Loe, 1964), 2. gingival index (GI) (Loe and Silness, 1963), 3. probing pocket depth (PPD), and 4. clinical attachment level (CAL). All this information was recorded at baseline and 3 months.

Periodontal therapy

All patients in this study were treated with scaling and root planing using an ultrasonic scaler and hand instruments (Gracey curettes, Hu-Friedy®, Chicago, IL, USA). Group B patients were treated with scaling, root planing, and linezolid hydrogel. Hydrogel was injected subgingivally into the periodontal pocket using a blunt cannula syringe. In both groups, periodontal dressing was placed. For one week, the participants were instructed not to use any interdental appliances, chew hard meals, or consume sticky foods. They were also told not to brush in the vicinity of the treated areas. After 1-week, periodontal dressing was removed. Patients were recalled for review after 3 months.

Statistical analysis

Using SPSS software, Version 23.0, statistical analysis was carried out. The normality distribution of data was done using the Shapiro-Wilk test. An independent t-test was used to evaluate the intergroup comparison. Within-group comparison between baseline and 3 months was analyzed by paired t-test. P value less than 0.05 was considered as a statistically significant difference.

Results and Discussion

In vitro analysis

Hemolysis assay

At varying hydrogel concentrations, the hemolysis ratio has been measured. The hemolysis ratio was less than 1% at a concentration of 2% and less than 2% at concentrations of 4%, 6%, 8%, and 10%. This result showed that the linezolid hydrogels had a low ratio of destruction of red blood cells **(Figure 1)**.

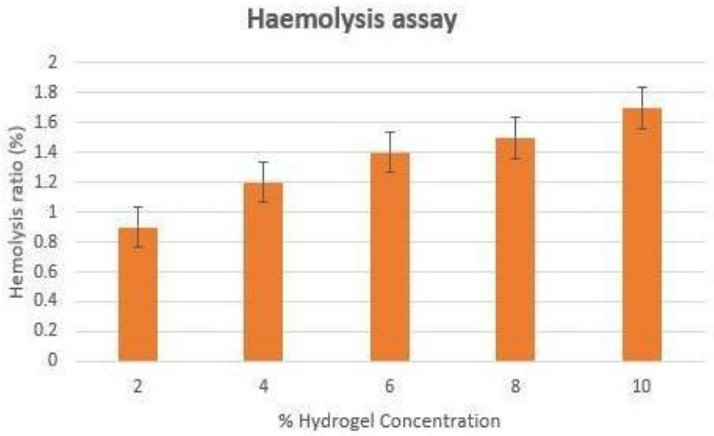

Figure 1. Hemolysis assay

Biocompatibility assay

Fibroblasts generated from human periodontal ligament tissue were exposed to varying concentrations of linezolid hydrogel for 24, 72, and 94 hours. The cell viability was then assessed using an MTT assay, and the data were normalized to cells that had not been exposed. Cell viability in the hydrogel was seen to decrease by up to 80% after 24 hours, 90% after 72 hours, and 98% after 94 hours. This indicates that linezolid hydrogel does not significantly harm human fibroblasts after 94 hours **(Figure 2)**.

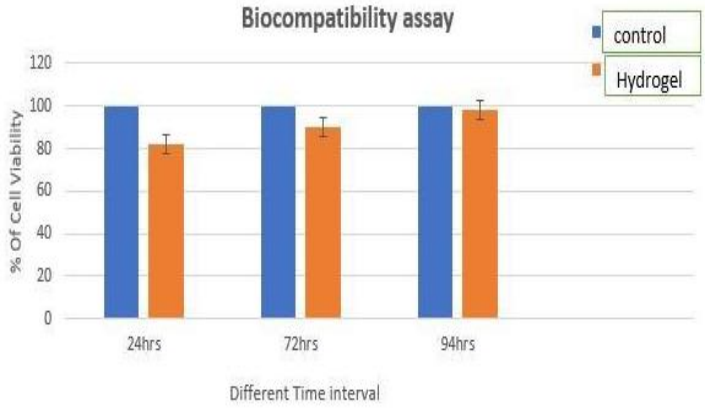

Figure 2. Biocompatibility assay

In vivo analysis

The clinical and demographic characteristics of both groups are presented in **Table 1**. Group A patients, who received simply scaling and root planing, had a mean age of 42.40 ± 3.27 years, PI and GI measurements of 2.63 ± 0.19 mm, PPD of 5.69 ±

0.36 mm, and CAL of 5.91 ± 0.38 mm. 11 women and 9 men participated. A mean age of 41.59 ± 3.35 years, PI of 2.67 ± 0.20 mm, GI of 2.63 ± 0.20 mm, PPD of 5.73 ± 0.39 mm, and CAL of 5.92 ± 0.41 mm were observed in patients treated with SRP and Hydrogel (group B). 9 women and 11 men participated.

Using independent t-tests, **Table 2** compares the two groups SRP (group A) and SRP with hydrogel (group B) at baseline and three months later. The two groups' baseline mean values for PI, GI, PPD, and CAL do not significantly differ from one another (P > 0.05). After three months, however, a statistically significant difference (p-value of 0.00) was found in favor of group B (SRP + Gel) over group A (SRP alone) in all parameters (PI, GI, PPD, and CAL).

Using paired t-tests, **Table 3** compares the two groups' baseline and three-month results. The PI value in group A decreased from 2.63 ± 0.19 mm to 1.29 ± 0.29 mm, the GI decreased from 2.60 ± 0.22 mm to 1.58 ± 0.31 mm, the PPD decreased from 5.69 ± 0.36 mm to 3.96 ± 0.70 mm, and the CAL decreased from 5.91 ± 0.38 mm to 4.18 ± 0.68 mm. All of the metrics (PI, GI, PPD, and CAL) showed significant differences (P-value < 0.05). PPD decreased from 5.73 ± 0.39 mm to 3.08 ± 0.34 mm, CAL decreased from 5.92 ± 0.41 mm to 3.27 ± 0.35 mm, GI decreased from 2.63 ± 0.20 mm to 0.72 ± 0.21 mm, and PI decreased from 2.67 ± 0.20 mm to 0.48 ± 0.20 mm in group B (SRP + Gel). All of the metrics (PI, GI, PPD, and CAL) showed significant differences (P-value < 0.05). At the three-month follow-up, group B had improved more than group A in every metric.

Table 1. Demographic and clinical characteristics of the study population of both groups

Parameter	Group A	Group B	P-value
Age (years)	42.40 ± 3.27	41.59 ± 3.35	0.62
Gender (Male/ Female)	9/11	11/9	0.41
PI	2.63 ± 0.19	2.67 ± 0.20	0.53
GI	2.60 ± 0.22	2.63 ± 0.20	0.60
PPD	5.69 ± 0.36	5.73 ± 0.39	0.74
CAL	5.91 ± 0.38	5.92 ± 0.41	0.96

Table 2. Comparison of clinical parameters between two groups by independent t-test

Parameters	Timeline	Group A (Mean ± SD)	Group B (Mean ± SD)	P-value
PI	Baseline	2.63 ± 0.19	2.67 ± 0.20	0.53
	3 month	1.29 ± 0.29	0.48 ± 0.20	0.00*
GI	Baseline	2.60 ± 0.22	2.63 ± 0.20	0.60
	3 month	1.58 ± 0.31	0.72 ± 0.21	0.00*
PPD	Baseline	5.69 ± 0.36	5.73 ± 0.39	0.74
	3 month	3.96 ± 0.70	3.08 ± 0.34	0.00*
CAL	Baseline	5.91 ± 0.38	5.92 ± 0.41	0.96
	3 month	4.18 ± 0.68	3.27 ± 0.35	0.00*

*Statistically significant at P-value < 0.05

Table 3. Comparison of mean clinical parameters between baseline and 3 months in group A and group B by paired t-test

Parameters	Timeline	Group A (Mean ± SD)	P-value	Group B (Mean ± SD)	P-value
PI	Baseline	2.63 ± 0.19	0.00*	2.67 ± 0.20	0.00*
	3 month	1.29 ± 0.29		0.48 ± 0.20	
GI	Baseline	2.60 ± 0.22	0.00*	2.63 ± 0.20	0.00*

	3 month	1.58 ± 0.31		0.72 ± 0.21	
PPD	Baseline	5.69 ± 0.36	0.00*	5.73 ± 0.39	0.00*
	3 month	3.96 ± 0.70		3.08 ± 0.34	
CAL	Baseline	5.91 ± 0.38	0.00*	5.92 ± 0.41	0.00*
	3 month	4.18 ± 0.68		3.27 ± 0.35	

*Statistically significant at P-value < 0.05

Local drug delivery has garnered a lot of interest and research lately for the treatment of periodontal disease. This technique delivers therapeutic chemicals straight to the site of inflammation or infection, allowing for the controlled and focused release of drugs. According to published research, linezolid prevents the production of biofilms and targets aerobes and anaerobes [12]. Studies have also demonstrated that hydrogels can deliver long-term, continuous medication release. It can stick to periodontal tissue, enabling targeted medication delivery in afflicted regions [19]. The purpose of this study was to create a linezolid-based hydrogel and assess how well it works as a locally administered medication for the treatment of stage II grade A periodontitis.

Good hemostatic ability and biocompatibility are two of the many qualities that make a suitable local drug delivery agent [26]. A hemolytic analysis and a biocompatibility test were conducted after the linezolid hydrogel was synthesized for the current investigation. Linezolid hydrogel has been found to have a modest ratio of red blood cell damage and is regarded as a non-significant hazardous chemical. The hydrogel that was created is a perfect local drug delivery agent, as demonstrated by the characterization analysis.

Linezolid in-situ gel was created and described by Goudanavar *et al*. to treat periodontitis. Using the cold approach, carbopol 934P and sodium carboxymethylcellulose and carbopol 934P and hydroxypropyl methylcellulose were combined to create a pH-sensitive in-situ gel. Before being subjected to an antibacterial activity test, the generated in-situ gels were evaluated for appearance, pH, gelling capability, viscosity, rheological investigations, in vitro release testing, and drug content estimation. The drug's compatibility with the physical mixture was demonstrated by the results. Drug release from the produced mixture lasted for 12 hours [27]. Additionally, Wassif *et al*. created a hydrogel that was evaluated in animal models of bone infections and contained spray-dried polymeric nanoparticles that contained both linezolid and nano-hydroxyapatite. The authors stated that they were able to control the bone infections within 2-4 weeks of the injection [28].

The manufactured linezolid hydrogel was put through a clinical trial among patients with stage II grade A periodontitis in the current investigation because it was established that linezolid was beneficial in treating bone infections. There was a significant reduction in clinical parameters like PI, GI, PPD, and CAL among patients treated with SRP and hydrogel when compared to patients with SRP alone. The current research's results cannot be directly compared to those of any other study since it is the first study of its type to assess the efficacy of linezolid hydrogel as a local drug delivery agent in the management of periodontitis. However, the current study's findings indirectly support those of earlier investigations in which individuals with periodontitis received local medication administration using different antibiotics as an adjuvant to SRP.

For individuals with periodontitis, Graca *et al*. used 2% minocycline as a local medication delivery technique; they observed a significant reduction in PD from baseline to 6 and 12 weeks [29]. Using 1% alendronate gel as a local drug delivery strategy led to a significant decrease in PD and CAL in the second and sixth months, according to Sharma *et al*. [30]. Additionally, improvements in periodontal parameters were documented when 3% satranidazole gel was utilized as an adjuvant to SRP [31]. Our results are consistent with earlier research.

Overall, the created linezolid hydrogel has demonstrated hemostatic and biocompatible qualities. In patients with stage II grade A periodontitis, the clinical investigation further indicates that linezolid hydrogel works well as a local drug delivery method when combined with scaling and root planing.

There aren't many restrictions on this study, though. Both the degradation rate and the release pattern are not analyzed in the in vitro study. Additionally, a limited number of patients participated in the clinical investigation. Therefore, to validate the study findings, more randomized controlled trials involving larger populations are required.

Conclusion

As an adjunct to SRP, locally administered linezolid gel appears to be effective in significantly improving clinical parameters such as plaque index, gingival index, probing pocket depth, and clinical attachment level in patients with stage II grade A periodontitis, according to the study findings.

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Conflict of interest: None

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Ethics statement: None

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