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Advance and Emerging Roles of Hydrogel in Promoting Periodontal Tissue Regeneration and Repairing Bone Defect

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ABSTRACT

Aim: This study was conducted to investigate the role of hydrogel on alveolar bone defect repairment of bone defect and promoting periodontal tissue Regeneration

Methods: For this clinical study, we recruited 23 patients (17 females and 6 males with a mean age of 50.3 years) who had moderate to advanced chronic periodontitis. Compromised systemic health condition and no contraindications for periodontal surgery . All study subjects had destruction of periodontal tissue and at least one 1-, 2- or 3-walled bone defect. Before periodontal surgical treatment, each patient received an initial preparatory session, including oral hygiene instruction, scaling, and root planing.

Results: The pre-treatment and post-treatment clinical parameters were evaluate and we compared the values of PPD, CAL, and LBG at 3, 6, and 12 months after treatment with the pre-treatment values. From before treatment to 12 months after treatment, the changes in mean PPD and mean CAL of treated sites were 3.8 ± 1.9 mm and 5.9 ± 2.0 mm, respectively. Also, at 12 months following treatment, hard tissue showed a mean LBG of 3.5 ± 2.1 mm and a mean BF of 61.8 ± 25.2%. The mean depth of bone defects and periodontal tissue regeneration was less at both 6 months and 12 months compared with the pre-treatment mean . These differences were statistically significant

Conclusion: The results demonstrated that the hydrogel successfully delivered periodontal ligament stem cells derived exosomes for repairing alveolar bone defects .

We evaluated the clinical effects of the sustained release of bFGF from gelatin hydrogel for the treatment of periodontal disease with infrabony defects and periodontal tissue regeneration . we obtain clinical attachment gain, probing depth reduction, and radiographic bone fill. We conclude by suggesting that the topical application of gelatin hydrogel in the treatment of chronic periodontitis with infrabony defects or furcation is safe, leads to improvement of clinical parameters, and offers promise as a new avenue for periodontal regeneration.

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1. INTRODUCTION

Periodontitis is a chronic, destructive inflammation characterized by microbial infection and accelerated loss of alveolar bone, ultimately resulting in the loss of teeth .[1] As the world ages, periodontitis has become one of the major oral diseases, affecting a significant number of people around the world. Epidemiological evidence shows that approximately 20–50% of the global population suffers from periodontal-related diseases, and approximately 10% of the global population is affected by severe periodontitis. periodontal tissue regeneration are essential for oral and general health. Periodontal tissue is the functional system surrounding teeth and has a complex hierarchical structure comprising hard and soft tissue together as a whole.[2] Periodontal tissue regeneration involves the reconstitution of periodontal ligament (PDL) and alveolar bone around the teeth and cementum . Traditional two-dimensional biomaterials, such as GTR barriers, provide adhesion sites and prevent soft tissue from growing into bone defects, but biological stimulation for functional cells is limited.[3]

Hydrogels are a new type of functional polymer material that has emerged in recent years. They are cross-linked three-dimensional hydrophilic polymer networks with properties superior to traditional materials, including softness, non-deformability, strong water absorption capacity, intelligence, high drug utilization rate, safety, and convenience.[4] However, single-component hydrogels have relatively simple structures, generally low mechanical strength, and only basic hydrogel properties, which cannot fully meet the needs of complex applications and have certain limitations. In recent years, the basic research and clinical applications of hydrogels have become increasingly rich, with great potential and unique therapeutic plasticity in promoting periodontal tissue regeneration and repairing bone defects. Firstly, hydrogels can provide a microenvironment similar to the extracellular matrix, allowing periodontal tissues and bone cells to adhere, proliferate, and differentiate. Secondly, hydrogels can serve as drug release carriers, exerting anti-inflammatory and antibacterial effects, and promoting periodontal tissue regeneration.[5] Additionally, hydrogels can also carry specific bioactive factors such as stromal cell-derived factor-1 (SDF-1) and bone morphogenetic proteins (BMPs), inducing them to differentiate into osteoblasts, thereby accelerating periodontal bone tissue regeneration. Hydrogels are currently one of the hottest research materials, and are expected to provide a new perspective for promoting periodontal tissue regeneration and repairing periodontal bone defects.[6]

Hydrogels can reduce the potential toxicities and side effects generally associated with drug-directed delivery, while also extending the local drug retention rate through their slow but gradual biodegradability and swelling properties in vivo. Furthermore, hydrogels exhibit multifunctional stimuli-responsive properties that can be triggered by various factors, such as pH , near-infrared (NIR) irradiation , reactive oxygen species (ROS) , and ultrasonic (US) stimulation at the lesion site. [7]This ensures the controllable release of bioactive molecules from the hydrogel network, avoiding the unnecessary waste of therapeutic agents. Therefore, hydrogel-based spatial/sequential delivery is a promising strategy for bone repair when aligned with the natural bone healing process. These advantages render hydrogels ideal delivery platforms for loading various therapeutic molecules either proper physical encapsulation or chemical conjugation.[8]

Hydrogels are three-dimensional water-swollen polymeric materials with superior biocompatibility, mechanical strength, and accessibility that have been widely used in biomedical applications such as cell culture , drug delivery , and tissue engineering . In tissue engineering, biomaterials provide a three-dimensional scaffold for cell adhesion, proliferation, and differentiation. [9]The scaffold should be a porous, three-dimensional, network-like structure providing cells with the necessary space to deposit their extracellular matrix while exchanging cellular substances with the surrounding environment. Due to their distinctive three-dimensional mesh structure, high porosity, superior hydrophilicity and viscoelasticity, and controllable compositions, hydrogels can mimic the microenvironment of the extracellular matrix, which is favourable for cell attachment, proliferation, and differentiation. Through combination with drugs , stem cells , or growth factors , hydrogels show significant potential in periodontal regeneration and have gained a considerable amount of attention in recent years. Periodontal tissue regeneration is a complex and sophisticated process.[10] Hydrogels have been widely applied as scaffolds for regenerative medicine and as a sustained-release system in periodontal tissue engineering. Current research has noted that the composition and structure of hydrogels have a significant impact on periodontal tissue regeneration. However, there is no paper summarizing these impacts which may pave the way for researchers to develop appropriate hydrogel designs in periodontal tissue engineering. Based on the above, this paper reviews the applications of hydrogels in periodontal tissue regeneration research and provides discussions and prospects about their future designs, with the objective of making a valuable contribution to successful periodontal tissue regeneration.[11] Bone tissue is a vital component of the human body, comprising one of the fundamental organ systems that provides essential support for movement, and playing a pivotal role in facilitating physical activity. Additionally, bone tissue can safeguard the vital organs and regulate the cellular metabolism. Consequently, maintaining the health of bone tissue is imperative for fostering social participation and is a critical determinant of an individual's quality of life . However, approximately 50% of adults, and particularly the aged population, experience bone injuries or defects . These issues are usually induced by trauma, diseases, and other factors . The gold standard treatments for bone repair predominantly involve autografts, allografts, and internal fixation . Although these approaches have gained widespread acceptance, certain drawbacks are evident, including the limited availability of donor tissues, risk of infection, potential immunogenicity, and other associated concerns .[12]

2. MATERIAL AND MATERIAL

For this clinical study, we recruited 23 patients (17 females

and 6 males with a mean age of 50.3 years) who had moderate

to advanced chronic periodontitis and who were scheduled to

receive periodontal therapy The study design and consent forms were approved

Exclusion Criteria:

a) a non-compromised systemic health condition and no contraindications for periodontal surgery

b) a probing attachment loss equal to or greater than 4 mm

c) Clinical and radiographic evidence of the presence of an interproximal defect with an infra bony component.

All study subjects had destruction of periodontal tissue and at least one 1-, 2- or 3-walled bone defect. Before periodontal surgical treatment, each patient received an initial preparatory session, including oral hygiene instruction, scaling, and root planning.

The gelatin used in this study is an acid gelatin hydrogel that has an adjusted isoelectric point of 5.0 with moisture content of 95%. It is of cow bone origin . The acid gelatin was freeze-dried, and a safety identification test and a sterility test were conducted gelatin hydrogel material was prepared before surgery, for every 20 mg of gelatin and was left standing afterwards for 24 hours at 4 ˚C. Surgical procedures Following local anaesthesia, intra-crevicular incisions were made extending to the neighbouring teeth. Then, full-thickness mucoperiosteal flaps were raised vestibular and orally. All granulation tissues were removed from defects and the roots were thoroughly scaled and planed by means of manual instruments. The defects and the adjacent mucoperiosteal flaps were then thoroughly rinsed with sterile saline, after which the defects were filled with gelatin hydrogel . After placing the hydrogel material, the flaps were repositioned and closed with sutures. Postoperative care All patients received antibiotics orally for 5 days following surgery. The sutures were removed 7 to 14 days after surgery.

The experimental outcomes of interest included soft-tissue and hard-tissue measurements of the intra-oral radiographs taken with a parallel technique:

a. Change in probing pocket depth (PPD)

b. Change in clinical attachment level (CAL)

c. Changes in the radiographic values of linear bone gain (LBG) and percentage of bone fill (BF) The values of LBG and BF were determined by measuring intraoral radiographs .LBG was determined by measuring the distance from the CEJ to the base of the defect at the baseline minus the distance from the CEJ to the base of the defect at each of the post-surgical time points. The radiographic rate of bone fill was calculated by dividing the LBG by the depth of the original bone defect. Statistical analysis For statistical evaluation of the change from baseline to 3, 6, and 12 months, we used the Wilcoxson signed-rank test.

3. RESULT

Table 1: Characteristics of study subjects.

Bone defect type	n	Female	Male	Mean age (years)
1 wallled	6	5	1	55.7
2 walled	10	6	2	56.4
3 walled	7	6	3	45.6

Table 2: Periodontal examinations.

	Before Treatment	3 Month	6 Month	12 Month
PPD	**6.7 ± 1.8.**	**0±1.7**	**3.2± 1.3 3**	**3.8±1.9**
CAL	**8.6±6**	**6.3±1.4**	**5.9±1.6**	**9±2.0**
LBG	**2.6 ± 1.4**	**1.6±0.8**	**2.7±1.6**	**3.5±2.1**
BF		**29.1±23.2**	**50.7±21.7**	**61.8±25.2**

PPD: probing pocket depth, CAL: clinical attachment level, LBG: radiographic linear bone gain, BF: radiographic bone fill

The characteristics of the subjects in this study are shown in Table 1. The bFGF/hydrogel dose ranged from 40 µg to 185 µg (mean 89.7 µg). All subjects completed the study; in all cases postoperative healing was uneventful. No allergic reactions, abscesses, infections, or other complications were observed during the study period. The pre-treatment and post-treatment clinical parameters are shown in Table 2. We compared the values of PPD, CAL, and LBG at 3, 6, and 12 months after treatment with the pre-treatment values. From before treatment to 12 months after treatment, the changes in mean PPD and mean CAL of treated sites were 3.8 ± 1.9 mm and 5.9 ± 2.0 mm, respectively. Also, at 12 months following treatment, hard tissue showed a mean LBG of 3.5 ± 2.1 mm and a mean BF of 61.8 ± 25.2%. The mean depth of bone defects was less at both 6 months and 12 months compared with the pre-treatment mean (Figure 1). These differences were statistically significant. In this case, the 12-month radiograph showed good bone fill compared with the pre-treatment radiograph.

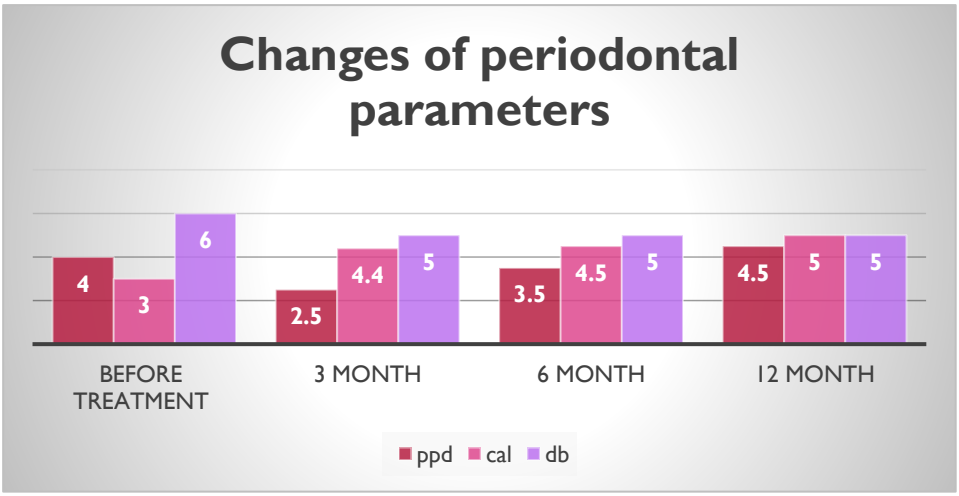

Figure 1: Changes of periodontal parameters. PPD: probing pocket depth, CAL: clinical attachment level, DB:depth of bone defect; *: significant difference from before treatment (p<0.05)

4. DISCUSSION

Gelatin, a denatured collagen, is obtained by acid and alkaline processing of collagen isolated from bovine bone. This processing affects the electrical nature of collagen, yielding gelatin with different isoelectric points (IEPs) [13,14]. When mixed with positively or negatively charged gelatin, an oppositely charged protein ionically interacts to form a polyion complex. When bFGF that has been ionically complexed to an acidic gelatin hydrogel is placed in a target site, the bFGF will be released after a periodas a result of hydrogel degradation [15]. The degradation is controllable by changing the extent of cross-linking, which, in turn, affects the water content of the hydrogel. The rate of bFGF release accords well with the rate of hydrogel degradation.Gelatin hydrogel releases the protein drug without interfering with biological activity [16]. The optimum water content for promoting bone formation without disturbing it due to unabsorbed gelatin is 90-98% [17]. In the present study, the water content of the hydrogel was 95%. The bFGF release period associated with hydrogel degradation was expected to be about 4 weeks. We had no trouble placing bFGF/ gelatin hydrogel in the target site without it flowing out into the surrounding tissue.

Gelatin hydrogel has already been used to clinically deliver bFGF to treat ischemic limb disease and Bell's palsy [18]. The mechanisms by which bFGF facilitates periodontal regeneration are thought to include angiogenic activity and a mitogenic effect on mesenchymal stem cells within the periodontal ligament [3]. We hypothesize that periodontal regeneration is promoted by the sustained release of bFGF from gelatin hydrogel. In addition, we suspect that gelatin plays a role as a scaffold in the early stage of periodontal tissue regeneration.In our clinical study, a marked improvement of the infrabony defect was observed at 6 months after treatment. The radiographic and clinical parameters were stable at 12 months after bFGF/ gelatin hydrogel treatment. It has been reported that the clinical parameters and radiographic findings were stable at 6 years after 0.3% bFGF treatment. This may have a higher capacity for new alveolar bone regeneration than other periodontal regenerative therapies.[19]

5. CONCLUSION

We evaluated the clinical effects of the sustained release of bFGF from gelatin hydrogel for the treatment of periodontal disease with infrabony defects. We conclude by suggesting that the topical application of bFGF/gelatin hydrogel in the treatment of chronic periodontitis with infra bony defects or furcation is safe, leads to improvement of clinical parameters, and offers promise as a new avenue for periodontal regeneration.

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