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A Clinical Study of Bone Morphogenetic Protein-2 for Socket Preservation after Tooth Extraction

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Abstract: Alveolar bone insufficiency is one of the difficulties in implantation, and socket preservation techniques can slow down alveolar bone resorption by intervention measures during tooth extraction. However, the standard method for socket preservation has not been unified yet due to the multiple selection of materials. Recombinant human bone morphogenetic protein-2 (rhBMP-2) has good osteoinductivity and can induce undifferentiated mesenchymal stem cells to differentiate and proliferate towards chondrocytes and osteoblasts. Here, we evaluated the clinical effects of recombinant human bone morphogenetic protein-2 for socket preservation after tooth extraction. The histological analysis revealed a significantly higher proportion of alveolar bone trabeculae in the rhBMP-2 group compared to the control group ($P<0.05$). The absorptions of alveolar bone width and height between the two groups at each time point showed no significant differences (all Ps > 0.05), except for the alveolar bone width absorption in the rhBMP-2 group at 3 months post-surgery, which was significantly better than that of the control group ($P < 0.05$). Additionally, the differences in bone mineral density changes, safety, and satisfaction evaluations between the two groups were not significant from pre-operation to 6 months postoperatively (all Ps > 0.05). In conclusion, rhBMP-2 used for socket preservation (bone wall defect $\leqslant$ 20%) can safely accelerate new bone formation, improve bone quality, and better maintain alveolar bone width for implantation at 3 months. Further investigation with larger sample sizes and long-term follow-ups is necessary to validate these findings.

1. Introduction

Dental implant restoration is gaining increasing popularity among patients due to its aesthetic appeal, high comfort, efficient mastication, and minimal impact on adjacent teeth. However, dental implant surgeries often encounter the challenge of insufficient soft and hard tissue at the implantation site. A systematic review conducted by Tan et al. [1] revealed that without intervention, natural healing of the extraction socket results in a horizontal bone loss of 29% to 63% and a vertical bone loss of 11% to 22% after 6 months, with 80% of alveolar bone loss occurring within 3 months.

To address this problem, some scholars have proposed socket preservation, which refers to the

extraction of a tooth before significant bone resorption occurs, followed by protective or reparative measures taken within the socket. These interventions aim to minimize physiological and pathological bone resorption by osteoclasts, promote new bone formation within the extraction socket, and improve the quality of the newly formed bone and mucosa. Socket preservation plays a crucial role in maintaining the volume and morphology of soft and hard tissues [2].

In a specific sense, socket preservation techniques mainly refer to the immediate placement of bone grafting materials within the socket and various methods of socket closure, such as covering with collagen membrane or soft tissue. Socket preservation techniques result in lower horizontal and vertical alveolar bone resorption rates, better maintenance of the buccal bone plate, and less loss of alveolar ridge bone, leading to improved aesthetic outcomes.

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is a bone-inductive growth factor that can be delivered through an acellular collagen sponge (ACS). It can be used alone or in combination with hydroxyapatite particles, decalcified bovine bone, ultrasound-induced silk hydrogel, bacterial cellulose, absorbable collagen sponge, and other carriers.

Compared to other carrier systems, rhBMP-2/ACS has significant advantages, and its feasibility and safety in socket preservation have been demonstrated [3/6]. Studies have shown that the use of rhBMP-2/ACS can regenerate part of the buccal bone plate and maintain alveolar bone mass even when 50% of the buccal cortical bone is resorbed, allowing for implant placement after five months postoperatively [4]. However, the current studies on socket preservation have used relatively high concentrations of rhBMP-2/ACS, typically 0.75mg/ml or 1.5mg/ml [5]. Low-dose rhBMP-2 has been used with dentin-derived matrix (DDM) [6], injectable decalcified bone matrix (DBM) [7], or demineralized bovine bone mineral (DBBM) as carriers [8]. The optimal dosage of rhBMP-2/ACS needs further optimization to strike a balance between efficacy and cost-effectiveness.

In this experiment, 0.3 mg rhBMP-2 was inserted into the extraction site, covered by a collagen sponge, to explore its clinical efficacy by comparing with the control group.

2. Materials and methods

2.1 General Information and Grouping

20 adult patients with posterior teeth suitable for extraction from February 2019 to March 2023 were selected for this randomized, controlled, and parallel-group clinical trial. Based on informed consent and voluntary participation, patients of any gender were randomized into two groups: A and B, with 10 cases in each group. Group A served as the control group, while Group B served as the experimental group. Prior to the start of implant treatment, both groups received socket preservation treatment. In Group A, a collagen sponge was placed into the extraction socket; in Group B, bone superior inductive material was implanted and covered with a collagen sponge. Approval was obtained from the Ethics Committee of Suzhou Stomatological Hospital. All patients signed informed consent forms before surgery.

2.2 Inclusion and exclusion criteria

Inclusion Criteria: I. Molars or premolars, bone wall defect ≤ 20 %, ideal soft tissue level; II. Socket bottom adjacent to the inferior alveolar canal, lack of adequate initial stability for immediate implant placement; III. Pre-existing bone resorption, bony wall defects, apical periodontitis, or combined periodontal-endodontic lesions causing bone destruction, where allowing natural socket healing would result in suboptimal bone healing or severe risk of alveolar ridge resorption.

Exclusion Criteria: I. Acute inflammatory period of the affected tooth, or poor periodontal condition of adjacent teeth without systemic treatment; II. Long-term use of non-steroidal anti-

inflammatory drugs, bisphosphonates, or corticosteroids that may affect bone healing; III. Alcohol consumption, heavy smoking, pregnancy, medically compromised patients, or history of head and neck radiation therapy, making the patient unsuitable for surgery; IV. Poor compliance, inability to attend follow-up appointments after surgery.

2.3 Experimental Protocol

After local anesthesia, perform a minimally invasive tooth extraction, avoiding buccal-lingual rocking forces. Remove residual inflammatory tissue and repeatedly irrigate with a saline solution. In Group A, implant a collagen sponge. In Group B, place bone superior inductive material 0.3mg in the socket and cover it with a collagen sponge. Ensure that the graft materials are level with the adjacent buccal and lingual crestal bone. Approximate flap closure, but complete socket closure is not required. Prescribe oral antibiotics for 3-5 days postoperatively and schedule regular follow-up visits. Three months post-surgery, bone-level implants were placed, and healing abutments were installed, with a follow-up examination at six months (see Figure 1).

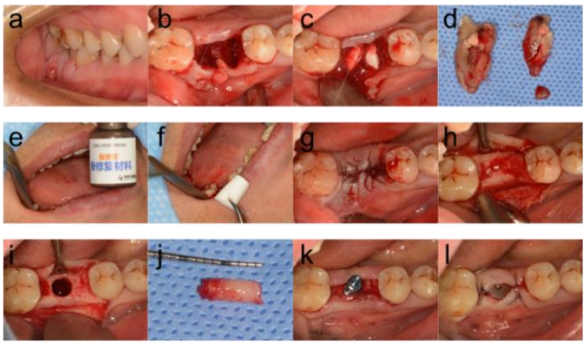


Figure 1: Tooth extraction (a-d), graft materials placement (e-g) and implant surgery process (h-l)

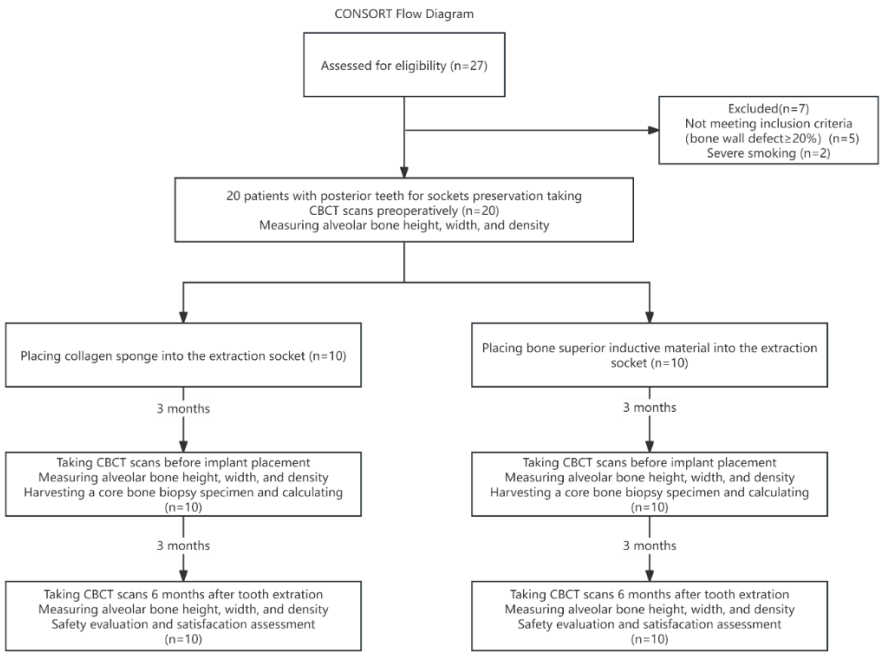


Figure 2: Flow diagram of a trial comparing control group and experimental group for socket preservation

Building on this, the study compared histological sections, the height and width of the alveolar bone, and the absorption conditions, changes in BMD at the extraction socket, complications, and satisfaction levels between the two groups receiving socket preservation treatment (see Figure 2).

2.4 Histological Evaluation

Three months after socket preservation surgery, an intraoral scan and CBCT data are used to design and fabricate a bone harvesting guide. Under the guidance of the surgical guide, a gingival punch technique is performed without flap reflection, and a trephine bur is used to harvest a core bone biopsy specimen from the crest towards the root. The biopsy specimen is prepared according to the standard method by Donath & Breuner (1982) for sectioning and VG staining. Immediately after harvesting, the trephine bur, along with the bone core, is immersed in 4% neutral formalin for 2 days, followed by rinsing with running water for 4 hours. The specimen is then dehydrated by immersing it in 75% ethanol for 2 days, 85% ethanol for 2 days, 95% ethanol for 2 days, and 100% ethanol for 2 days. After immersion in xylene for 60 minutes, the specimen is embedded in methyl methacrylate. Using a German-made LEICA SP1600 microtome, sections are cut to a thickness of 120 μm, mounted onto slides using German-made 201 adhesive, and ground down to 50 μm after 24 hours using 1200 grit sandpaper. The sections are then polished with alumina suspension, rinsed with running water, immersed in 0.1% formalin for 3 minutes, rinsed with running water for 2 minutes, blotted dry, immersed in 20% ethanol for 2 hours, rinsed with running water for 2 minutes, blotted dry, and stained with alizarin red. Finally, the sections are mounted with neutral resin (see Figure 3).

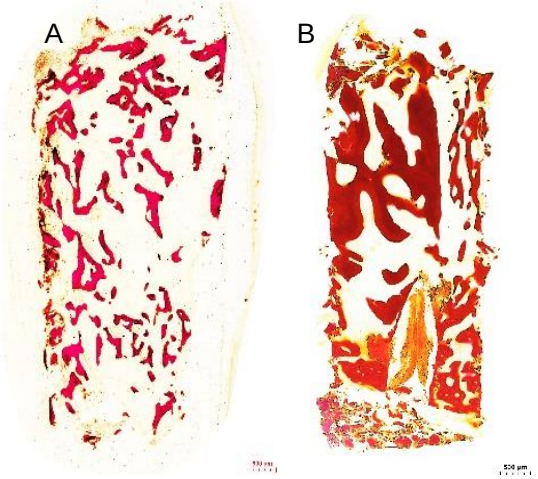


Figure 3: Control group section (A) and experimental group section (B)

Each section is observed under an inverted microscope. Within the area of each section, three fields of view with an area of 0.5 mm^2 are randomly selected for measurement and analysis. Professional image analysis software is used to automatically calculate the volume fractions of alveolar bone trabeculae based on pixel analysis within the selected fields of view.

2.5 Alveolar Bone Height, Width, and Changes

Take CBCT scans preoperatively (D1), 3 months postoperatively before implant placement (D2), and 6 months postoperatively (D3). Export and save the CT data in '.DICOM' format.

D1: Adjust the sagittal and coronal 3D positions, select the slice passing through the center of the extraction socket, and choose the inferior alveolar nerve canal or the sinus floor as a fixed reference point, assuming a horizontal line. Measure the distance from the buccal alveolar crest to the line as the buccal alveolar ridge height Hb1, and the distance from the lingual (palatal) alveolar crest to the

line as the lingual (palatal) alveolar ridge height HL l. Measure the distance between the buccal and lingual (palatal) alveolar crests as the alveolar ridge width W1.

D2, D3: Select the same slice as D1, mark the fixed reference point, draw the corresponding reference lines, and measure the buccal and lingual (palatal) alveolar ridge heights Hb2, Hb3 and HL2, HL3, as well as the alveolar ridge widths W2, W3 (see Figure 4).

The radiographic landmarks and measurements are performed under the guidance of a radiologist. All measurements are performed by the same clinician. Calculate the corresponding Hb, HL, W values and their changes during the D1-D2, D1-D3, and D2-D3 periods.

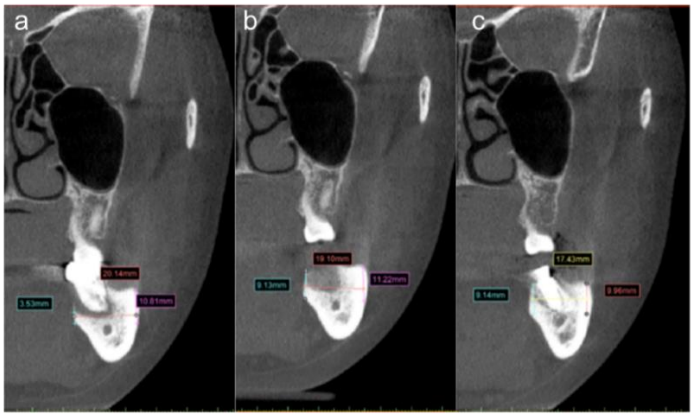
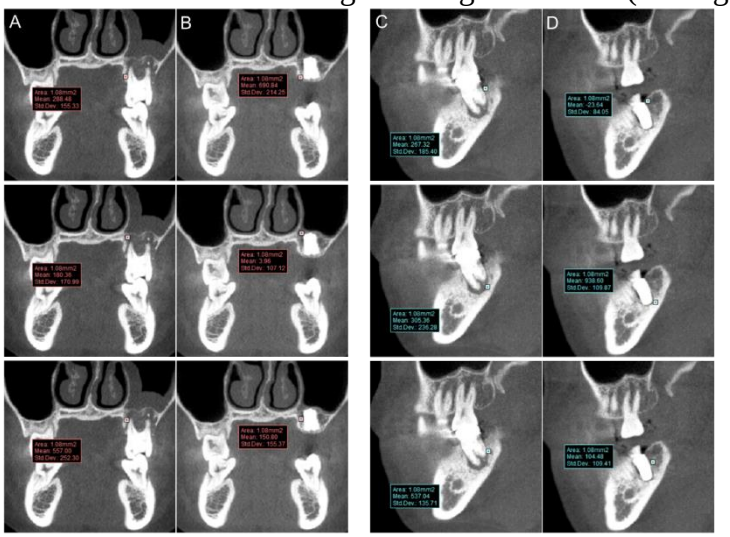


Figure 4: CBCT scan pre-surgery (a), 3 months post-surgery (b) and 6 months post-surgery (c)

2.6 Alveolar Bone Mineral Density changes

D1: The bone mineral density (BMD) at the mesial, distal, labial, and lingual (palatal) sites of the affected tooth is measured. The BMD values at each site are respectively measured at the crest of the alveolar ridge, at the apex of the root, and at the midpoint between the two points. The mean values of the 3 points are taken as the BMD values at this site, and the mean values at the mesial, distal, labial, and lingual sites are taken as the BMD values of this tooth as T1 [9].

D3: BMD is measured at the same location as T3 according to the above method. Measure BMD at the same location as T3. Calculate BMD changes during the D1-D3 (see Figure 5).



Palatal site, pre-surgery (A) and 6 months post-surgery (B)
Distal site, pre-surgery (C) and 6 months post-surgery (D)

Figure 5: BMD measuring

2.7 Safety evaluation

Observe intraoperatively and postoperatively for any complications such as immune reactions, facial swelling, oral erythema, significant neurovascular damage, postoperative infection, or peri-implantitis [10].

2.8 Satisfaction Assessment

Use the visual analog scale (VAS) to evaluate patient satisfaction. Scoring criteria: Use a sliding 10 cm ruler with 10 markings, with the ends representing '0' and '100' respectively, where 0 indicates disappointment and 100 indicates complete satisfaction. The VAS value is the distance between the patient's marked satisfaction point and 0. Patients self-evaluate their satisfaction based on intraoperative, postoperative, and masticatory function, as well as quality of life, with higher scores indicating greater satisfaction [11].

2.9 Statistical Methods

Use SPSS 27.0 software for data analysis. The measurement data are presented as mean ±standard deviation ($x \pm s$). One-way ANOVA and Student's t-test are used for inter-group comparisons of corresponding variables. A P-value ≤ 0.05 is considered statistically significant for drawing scientific conclusions.

3. Result

3.1 Study Population

During this clinical trial, 27 patients with posterior tooth for socket preservation were performed in the hospital. 7 patients could not be enrolled, including 5 patients with bone wall defect of more than 20% and 2 patients smoking severely. Twenty patients with 20 sites were included in this trial, with 10 patients enrolled in each group (see Table 1).

Table 1: Patient characteristics

	Control group (Group A)	Experimental group (Group B)
Gender	6 males and 4 females	7 males and 3 females
Age	38.1±9.39(24-52)	41.3±9.90(26-57)
Site	9 molars and 1 premolar	9 molars and 1 premolar
Hypertension	0	1(<140/100 mmHg)

3.2 Histological Observation

The 3-month post-surgery specimens were subjected to histological examination (see Figure 6). As shown in Table 2, the fraction of alveolar bone trabeculae in group B was 67.25±11.34 %, significantly higher than 53.95±12.80 % in group A ($P=0.024$, $P < 0.05$).

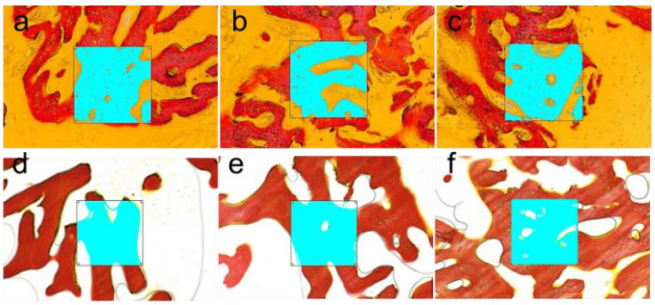


Figure 6: Calculating one section from Group A (a-c) and one section from Group B (d-f)

Table 2: Histological analysis

	Control group (Group A)	Experimental group (Group B)
BV/TV (%)	53.95±12.80	67.25±11.34
F (one-way ANOVA)		6.056
P (one-way ANOVA)		0.024

3.3 Alveolar Bone Height, Width, and Changes

The absorptions of alveolar bone width and height of the two groups in Table 3 showed no significant differences (all Ps>0.05), except that the absorption of alveolar bone width of group B from D1 to D2 was significantly smaller than that of group A (P=0.016, P<0.05).

Table 3: D1-D2, D2-D3, D1-D3 height and width changes

		Buccal height change (mm)		Lingual/Palatal height change (mm)		Width change (mm)	
		Control group (Group A)	Experimental group (Group B)	Control group (Group A)	Experimental group (Group B)	Control group (Group A)	Experimental group (Group B)
D1-D2		−0.51±2.00	0.16±1.17	0.06±1.44	0.55±1.94	−0.94±1.68	0.71±1.02
	F (one-way ANOVA)		0.842		0.396		7.049
	P (one-way ANOVA)		0.371		0.537		0.016
D2-D3		-0.65±1.36	-0.49±0.96	0.12±2.12	0.00±2.16	-0.36±0.94	-0.85±1.75
	F (one-way ANOVA)		0.090		0.004		0.608
	P (one-way ANOVA)		0.768		0.908		0.446
D1-D3		-1.16±1.97	-0.23±1.40	0.18±2.04	0.72±2.68	-1.30±1.16	-0.42±1.15
	F (one-way ANOVA)		1.474		0.258		2.864
	P (one-way ANOVA)		0.240		0.618		0.108

3.4 Alveolar Bone Mineral Density Changes

The average T1-T3 BMD change of group A was -20.09±163.05, while the figure was 1.04±235.52 in group B. There was no significant difference between Group A and Group B in Table 4 (P=0.818, P > 0.05).

Table 4: D1-D3 BMD changes

	Control group (Group A)	Experimental group (Group B)	F (one-way ANOVA)	P (one-way ANOVA)
Mesial site	-167.63±210.27	-195.22±444.29	0.032	0.861
Distal site	-205.42±199.11	-69.75±453.75	0.004	0.948
Buccal site	82.54±462.55	42.67±336.45	0.049	0.828
Lingual/palatal site	210.14±205.37	226.45±211.47	0.031	0.863
Tooth site	-20.09±163.05	1.04±235.52	0.054	0.818

3.5 Complications

Postoperative gingival healing in all cases was good, no wound split, obvious infection, graft loss,

or other conditions were found. The postoperative pains matched the degree of surgical trauma.

3.6 Satisfaction Assessment

The average VAS score in group A was 96.33±3.20 and 94.84±1.67 in group B. There was no significant difference between these two groups (P=0.24, P > 0.05).

3.7 Discussion

The collagen sponge used in this study was thought to have no effect on the preservation of bone tissue, and its main function is local hemostasis and soft tissue closure. In order to further verify the practical application of rhBMP-2 for site preservation, during the period of this study, the patients in Group B received relevant treatment intervention during the course of treatment.

RhBMP-2 promotes the differentiation of periodontal ligament cells into osteoblasts, stimulates alveolar bone regeneration, and has been proven to have excellent bone-inductive properties. Bone superior inductive material is a kind of absorbable bone-inductive substitute material made in China, mainly composed of rhBMP-2, using collagen sponge and hydroxyapatite as carriers.

Jung et al. suggested that 4-6 months post-surgery were suitable for implantation after using bone graft material and free gingiva or collagen mixture to seal the socket when the bone defect of the extraction site was less than 50% [12]. However, Shim et al. placed demineralized bovine bone and rhBMP-2 separately within the extraction socket, and the histological and radiographic examination results after three months showed that both materials successfully preserved the alveolar bone, but the rhBMP-2 group exhibited more new bone formation [13]. According to histological evaluation, this clinical trial found that 3 months after surgery, the rhBMP-2 group had a higher proportion of trabecular area, which meant better bone formation quality for implantation.

CBCT, one of the most commonly used auxiliary examinations, provides cross- sectional images that demonstrate high accuracy and reliability for bony linear measurements on cross- sectional images related to implant treatment [14]. The radiological examination in this trial found that the rhBMP-2 group had a significant difference in maintaining the width of the alveolar ridge at 3 months post-surgery, compared to the collagen sponge group, which was consistent with the findings of Lee and Araújo. Lee et al. found that the application of rhBMP-2 with a certain concentration in socket preservation surgery is beneficial for maintaining the width of the alveolar ridge and reducing absorption of the buccal bone plate [8]. Other researchers suggest that rhBMP-2 mainly reduces the width absorption of the remaining alveolar bone and has a lesser effect on reducing height absorption [15].

However, 6 months after socket preservation, there were no significant differences between the two groups based on alveolar bone absorption or bone mineral density change. This may be because rhBMP-2 is predominantly an osteoinductive material with a weak scaffold function, and thus the new bone is relatively easy to absorb.

Both groups did not find any serious complications such as allergies, swelling, wound splitting, peri-implant issues, etc. Additionally, the satisfaction evaluation did not show any significant difference either.

3.8 Conclusion

In conclusion, rhBMP-2 used for socket preservation (bone wall defect ≤ 20 %) can safely accelerate new bone formation, provide better bone quality, and maintain alveolar bone width better for implantation at 3 months. Further investigation with larger samples and long-term follow-ups is needed to further validate the accuracy of the experiment.

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