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Synergistic Effects of BMP-2 and VEGF with Calcined Bovine Bone for Alveolar Ridge Preservation: A Randomized Controlled Clinical Trial

Yinhua Xia[1], Renmei Hu[1], Shushu Liu[1], Yuling Luo[1], Youde Hu[1] & Guohui Wu[2]

[1] Department of Stomatology, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, 152 Aiguo Road, Nanchang, Jiangxi Province 330006, China

[2] The Affiliated Eye Hospital, Jiangxi Medical College, Nanchang University, China

Correspondence: Guohui Wu, The Affiliated Eye Hospital, Jiangxi Medical College, Nanchang University, BaYi Road No. 463, DongHu District, NanChang 330006, Jiangxi, China. E-mail: 13879187865@163.com

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Abstract

Background: Alveolar ridge remodeling following tooth extraction can result in significant dimensional loss, compromising future implant placement. While calcined bovine bone (CBB) has shown promise in socket preservation, the synergistic effects of combining CBB with bone morphogenetic protein-2 (BMP-2) and vascular endothelial growth factor (VEGF) remain inadequately studied.

Objective: To evaluate the clinical efficacy of different growth factor combinations with CBB for alveolar ridge preservation following tooth extraction through a randomized controlled trial.

Methods: Eighty patients requiring molar or premolar extraction were randomly allocated into four groups (n=20 each): control (no treatment), CBB alone, CBB+BMP-2, and CBB+BMP-2+VEGF. Primary outcomes included alveolar ridge dimensional changes assessed by cone-beam computed tomography at baseline and 3 months post-extraction. Secondary outcomes encompassed soft tissue healing evaluation using the Landry Wound Healing Index, pain assessment via Visual Analog Scale, and patient satisfaction scores. Bone density was evaluated through grayscale analysis of CBCT images.

Results: All groups showed comparable baseline characteristics. At 3 months, the CBB+BMP-2+VEGF group demonstrated superior ridge preservation with minimal buccal height loss (0.25±0.03 mm vs. 2.33±0.24 mm in controls, $p<0.01$) and optimal width preservation across all measurement levels. Hounsfield unit values increased most significantly in the combination group (1093.94±42.63 HU increase vs. 526.87±93.50 HU in controls, $p<0.01$). The CBB+BMP-2+VEGF group achieved significantly lower pain scores throughout the observation period, enhanced soft tissue healing scores, and higher patient satisfaction ratings (9.2±0.6 vs. 7.5±1.1 in controls, $p<0.05$).

Conclusions: The combination of CBB with BMP-2 and VEGF provides superior alveolar ridge preservation compared to conventional approaches, demonstrating enhanced dimensional stability, accelerated healing, and improved patient-reported outcomes. These findings support the clinical implementation of growth factor-enhanced socket preservation protocols for optimal implant site development.

Keywords: alveolar ridge preservation, bone morphogenetic protein-2, vascular endothelial growth factor, calcined bovine bone, socket preservation, implant dentistry

1. Introduction

Following tooth extraction, alveolar ridge remodeling represents a physiological but clinically challenging process that can significantly compromise future implant placement and prosthetic rehabilitation. Studies demonstrate that within the first year post-extraction, mean ridge width reduction can reach up to 50%, with an average loss of 3.87 mm horizontally and 1.67-2.03 mm vertically, with two-thirds of this resorption occurring within the first three months [1]. This dimensional loss not only affects the structural integrity of the alveolar ridge but also presents substantial challenges for optimal implant positioning and esthetic outcomes. Alveolar ridge preservation (ARP) techniques have therefore emerged as essential interventions to minimize post-extraction bone loss and maintain adequate bone volume for future implant therapy [2]. Among various biomaterials available for socket preservation,

calcined bovine bone (CBB) has gained attention due to its excellent biocompatibility and osteoconductive properties, while bone morphogenetic protein-2 (BMP-2) has been recognized as a potent osteoinductive growth factor with FDA approval for certain bone regeneration applications [3]. Additionally, vascular endothelial growth factor (VEGF) plays a crucial role in angiogenesis and bone repair processes, with studies demonstrating its essential function in coupling osteogenesis to angiogenesis during bone healing [4].

Despite the individual success of these biomaterials and growth factors, a significant research gap exists regarding the synergistic effects of combining CBB with both BMP-2 and VEGF for alveolar ridge preservation. While previous studies have demonstrated the efficacy of BMP-2 in promoting bone formation when used with various carrier materials, systematic reviews indicate that optimal dosing, delivery methods, and combination strategies remain inadequately defined(3). Similarly, although VEGF has shown promise in enhancing angiogenesis and bone repair in experimental models, its clinical application in socket preservation procedures has been limited [5]. The innovative aspect of this research lies in investigating the combined application of these three components, hypothesizing that VEGF-induced neovascularization may provide an optimal microenvironment for BMP-2-mediated osteogenesis, while CBB serves as an ideal osteoconductive scaffold. This combination strategy addresses the fundamental biological requirement that successful bone regeneration depends on both adequate blood supply and osteoinductive signals, potentially offering superior outcomes compared to individual component use. Furthermore, most existing studies have focused on comparing different materials rather than exploring optimal combinations, leaving a critical knowledge gap in understanding how these components interact synergistically to enhance bone preservation and soft tissue healing.

The primary objective of this randomized controlled clinical trial was to systematically evaluate the clinical efficacy of different growth factor combinations with CBB in alveolar ridge preservation following tooth extraction. Specifically, this study aimed to compare the effectiveness of CBB alone, CBB combined with BMP-2, and CBB combined with both BMP-2 and VEGF in preserving alveolar ridge dimensions and promoting optimal healing outcomes. To achieve these objectives, we employed a prospective, randomized, single-blind clinical trial design involving 80 patients requiring molar or premolar extraction, who were randomly allocated into four treatment groups: control (no treatment), CBB alone, CBB+BMP-2, and CBB+BMP-2+VEGF. The primary outcome measures included radiographic assessment of alveolar ridge dimensional changes using cone-beam computed tomography (CBCT) at baseline and 3 months post-extraction, while secondary outcomes encompassed soft tissue healing evaluation using the Landry Wound Healing Index, pain assessment via Visual Analog Scale, and patient satisfaction scores. Additionally, bone quality assessment was performed through grayscale analysis of CBCT images to evaluate new bone formation and mineralization patterns. This comprehensive evaluation methodology was designed to provide robust evidence regarding the optimal combination of growth factors with CBB for alveolar ridge preservation, ultimately informing evidence-based clinical decision-making and potentially improving patient outcomes in implant dentistry.

2. Methods

2.1 Study Design and Ethical Approval

This study was conducted as a prospective, randomized, single-blind controlled clinical trial to evaluate the efficacy of different growth factor combinations with calcined bovine bone (CBB) for alveolar ridge preservation following tooth extraction. The study protocol was reviewed and approved by the Institutional Review Board of Jiangxi Provincial People's Hospital (The First Affiliated Hospital of Nanchang Medical College) prior to patient enrollment. All procedures were performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants after thorough explanation of the study objectives, procedures, potential risks, and benefits. Patients were informed of their right to withdraw from the study at any time without affecting their standard dental care. The study followed the CONSORT guidelines for reporting randomized controlled trials to ensure transparency and methodological rigor.

2.2 Participants and Selection Criteria

A total of 80 patients requiring tooth extraction were recruited from the Department of Stomatology at Jiangxi Provincial People's Hospital. Inclusion criteria comprised (Table 1): age ≥20 years, requirement for extraction of a molar or premolar tooth, presence of at least one neighboring tooth at the extraction site, satisfactory oral hygiene (bleeding on probing <20%, plaque index <20%), good general systemic health without contraindications to oral surgical procedures, treatment intent for implant-retained prosthetic rehabilitation after extraction, and provision of signed informed consent. Exclusion criteria included (Table 2): individuals under legal age or with cognitive impairment unable to comprehend the study content, severe systemic conditions precluding routine outpatient extraction and implantation, previous radiotherapy for head and neck malignancies, prolonged use of

corticosteroids or bisphosphonates or other medications impairing bone regeneration, advanced periodontitis or inadequate oral hygiene, individuals smoking more than 10 cigarettes per day, and presence of acutely infected teeth. All participants underwent comprehensive medical and dental history review, clinical examination, and radiographic assessment to confirm eligibility before enrollment.

Table 1. Inclusion and Exclusion criteria

Inclusion	Exclusion
Age≥20 years	Individuals under legal age or with cognitive impairment who are unable to comprehend the content of the experiment
Requirement for extraction of a molar or premolar	Severe systemic conditions that preclude the ability to undergo routine outpatient extraction and implantation
Existence of one neighboring tooth at the extraction site	Previous radiotherapy for head and neck malignancies
Satisfactory oral hygiene (bleeding on probing <20%; plaque index <20%)	Prolonged use of corticosteroids, bisphosphonates, or other medications that impair bone regeneration
General systemic health without contraindications to oral surgical procedures	Advanced periodontitis or inadequate oral hygiene
Treatment intent for implant-retained prosthetic rehabilitation after extraction	Individuals who smoke more than 10 cigarettes per day
Provision of a signed informed consent form	Presence of acutely infected teeth

2.3 Randomization and Group Allocation

Eligible participants were randomly allocated into four treatment groups using a computer-generated randomization sequence with block randomization to ensure balanced group sizes. The four groups consisted of: Control group (n=20) receiving no socket preservation treatment, CBB group (n=20) receiving calcined bovine bone alone, CBB+BMP-2 group (n=20) receiving calcined bovine bone combined with bone morphogenetic protein-2, and CBB+BMP-2+VEGF group (n=20) receiving calcined bovine bone combined with both BMP-2 and vascular endothelial growth factor. Randomization was performed by an independent research coordinator not involved in patient treatment or outcome assessment. Group allocation was concealed using sealed, opaque envelopes that were opened only at the time of surgery. The treating surgeon was informed of the treatment allocation immediately before material placement, while outcome assessors remained blinded to group assignment throughout the study period. Baseline demographic and clinical characteristics were recorded for all participants to ensure comparability between groups.

2.4 Surgical Procedures

All surgical procedures were performed by a single experienced oral and maxillofacial surgeon to minimize inter-operator variability and ensure consistent technique. Patients received local anesthesia using 2% lidocaine with 1:100,000 epinephrine, and tooth extraction was performed using minimally traumatic techniques to preserve the integrity of the socket walls. Following extraction, the socket was thoroughly debrided and irrigated with sterile saline solution to remove any debris or granulation tissue. For the control group, no additional treatment was provided, and the socket was allowed to heal naturally with primary closure when possible. In the CBB group, the extraction socket was filled with calcined bovine bone particles (particle size 0.25-1.0 mm) to the level of the alveolar crest. The CBB+BMP-2 group received the same bone graft material combined with recombinant human BMP-2 at a concentration of 1.5 mg/mL according to manufacturer recommendations. The CBB+BMP-2+VEGF group received calcined bovine bone combined with both BMP-2 (1.5 mg/mL) and recombinant human VEGF (50 ng/mL) prepared according to standardized protocols. All grafted sites were covered with a resorbable collagen membrane and sutured with non-resorbable sutures for primary closure when possible.

2.5 Outcome Measurements and Follow-up Protocol

Primary outcome measures included radiographic assessment of alveolar ridge dimensional changes using cone-beam computed tomography (CBCT) performed immediately post-operatively and at 3 months following extraction. Standardized CBCT imaging protocols were employed with consistent patient positioning and exposure parameters to ensure measurement accuracy and reproducibility. Vertical ridge resorption was evaluated at two distinct anatomical sites: the buccal aspect (Hb) and the palatal/lingual aspect (Hp) of the alveolar ridge, with measurements taken from standardized reference points to the alveolar crest. Horizontal ridge width measurements

were systematically obtained at three predetermined levels: 3 mm, 8 mm, and 12 mm apical to the original alveolar bone crest, providing comprehensive assessment of ridge dimensional changes throughout the healing period. Bone density evaluation was performed through grayscale analysis within the socket preservation area, specifically targeting the central region of the extraction socket where treatment materials were placed. For grayscale measurements, standardized regions of interest were selected within the preserved socket area, and measurements were repeated three times at each site with the final value calculated as the mean of these repeated assessments to ensure measurement reliability. Volumetric analysis was performed using specialized imaging software to calculate total bone volume changes and assess the overall three-dimensional preservation of the alveolar ridge architecture.

Secondary outcome measures encompassed clinical evaluation of soft tissue healing using the Landry Wound Healing Index (LWHI) assessed at 1, 2, and 3 weeks post-operatively, with scores ranging from 1 (very poor healing) to 5 (excellent healing). Pain assessment was conducted using a Visual Analog Scale (VAS) ranging from 0 to 10, recorded on days 1, 3, and 7 post-operatively to monitor patient comfort and recovery progression. Patient satisfaction was evaluated at 3 months using a standardized questionnaire with scores from 1 (very unsatisfied) to 10 (very satisfied), assessing overall treatment experience and perceived outcomes. All clinical assessments were performed by calibrated examiners blinded to treatment allocation, and inter-examiner reliability was established through pilot testing prior to study commencement. Radiographic measurements were performed by a single trained examiner using consistent measurement protocols, with a subset of images re-measured to assess intra-examiner reliability and ensure measurement precision throughout the study period.

2.6 Statistical Analysis

Statistical analysis was performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA) with significance set at $p<0.05$ for all comparisons. Descriptive statistics including means, standard deviations, frequencies, and percentages were calculated for all variables. Normal distribution of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of histograms and Q-Q plots. Between-group comparisons of baseline characteristics were performed using one-way ANOVA for continuous variables and Fisher's exact test for categorical variables to confirm successful randomization. Primary outcome measures (ridge dimensional changes) were analyzed using repeated measures ANOVA to assess changes over time and between groups, with post-hoc pairwise comparisons performed using Bonferroni correction for multiple testing. Secondary outcomes including LWHI scores, VAS pain scores, and patient satisfaction were compared between groups using appropriate parametric or non-parametric tests based on data distribution. Effect sizes were calculated where appropriate, and 95% confidence intervals were provided for all estimates to facilitate clinical interpretation of results.

3. Results

3.1 Baseline Patient Characteristics

A total of 80 patients were enrolled and randomly allocated into four treatment groups, with 20 patients in each group. The baseline demographic and clinical characteristics were well-balanced across all groups, demonstrating successful randomization (Table 2). The gender distribution showed no significant difference between groups ($p = 0.92$), with a relatively even split between male and female participants across all treatment arms. The mean age of participants ranged from 47 ± 9 years in the control group to 50 ± 8 years in the CBB+BMP-2 group, with no statistically significant difference observed between groups ($p = 0.18$). Regarding tooth position, the distribution between first and second molars was comparable across all groups ($p = 0.85$), ensuring that anatomical variations would not confound the treatment outcomes. Similarly, the reasons for tooth extraction were evenly distributed among the groups ($p = 0.96$), with residual root and crown being the most common indication, followed by tooth fracture and chronic periapical lesions. These baseline comparisons confirm that the randomization process was effective in creating homogeneous groups, thereby minimizing potential confounding variables that could influence the study outcomes.

Table 2. Baseline characteristics of the enrolled patients

Characteristics	Control group (n=20)	CBB group (n=20)	CBB+BMP-2 group (n=20)	CBB+BMP-2+ VEGF group (n=20)	P value
Gender (male/female) (n)	11/9	12/8	10/10	9/11	0.92[a]

Age (years, mean ± SD)	47 ± 9	49 ± 10	50 ± 8	48 ± 7	0.18[b]
Tooth position (first molar/second molar) (n)	12/8	11/9	13/7	10/10	0.85[a]
Reason for extraction (residual root and crown/tooth fracture/chronic periapical lesion) (n)	10/6/4	9/7/4	8/6/6	11/5/4	0.96[a]

[a]Fisher exact test

[b]One-Way ANOVA

3.2 Alveolar Ridge Dimensional Changes and Bone Density

At baseline, all measured parameters showed no significant differences between the four treatment groups, confirming successful randomization. The buccal height (Hb) ranged from 17.18 ± 1.21 mm in the control group to 17.25 ± 1.18 mm in the CBB+BMP-2 group ($p = 0.892$). Similarly, palatal height (Hp) measurements were comparable across groups, ranging from 16.79 ± 1.31 mm to 16.88 ± 1.25 mm ($p = 0.785$). Ridge width measurements at the crest (W1), 3mm apical (W2), and 6mm apical (W3) levels also demonstrated no baseline differences between groups ($p = 0.915$, 0.685, and 0.825, respectively). Bone density values (Hu) were consistent across all groups, ranging from 1358.45 ± 42.18 to 1365.28 ± 41.65 Hounsfield units ($p = 0.892$).

At three months post-extraction, significant differences emerged between treatment groups across all measured parameters ($p < 0.01$ for height, width, and bone density measurements; $p < 0.05$ for W3). The CBB+BMP-2+VEGF group demonstrated superior preservation of alveolar ridge dimensions compared to all other groups.

Buccal height reduction was most pronounced in the control group (2.33 ± 0.24 mm loss) and progressively decreased with treatment intensity. The CBB group showed 1.56 ± 0.21 mm loss, the CBB+BMP-2 group demonstrated 0.97 ± 0.04 mm loss, while the CBB+BMP-2+VEGF group achieved the best preservation with only 0.25 ± 0.03 mm loss. A similar pattern was observed for palatal height, where the control group lost 3.26 ± 0.14 mm compared to 0.76 ± 0.03 mm in the combination treatment group.

Ridge width changes followed a consistent pattern across all measurement levels. At the crest level (W1), the control group experienced 2.37 ± 0.06 mm reduction, while the CBB+BMP-2+VEGF group showed only 0.71 ± 0.16 mm reduction. At 3mm apical (W2), reductions ranged from 3.30 ± 0.57 mm in controls to 0.80 ± 0.14 mm in the combination group. Even at the 6mm apical level (W3), where changes were generally smaller, the combination treatment group (0.50 ± 0.03 mm reduction) significantly outperformed the control group (2.16 ± 0.30 mm reduction).

Hounsfield unit values increased in all groups, indicating new bone formation and mineralization. However, the magnitude of increase was treatment-dependent. The control group showed a modest increase of 526.87 ± 93.50 HU, while the CBB+BMP-2+VEGF group demonstrated the highest increase of 1093.94 ± 42.63 HU. The CBB and CBB+BMP-2 groups showed intermediate improvements of 691.95 ± 82.61 HU and 920.17 ± 56.60 HU, respectively.

Table 3. Changes in alveolar ridge height, width, and grayscale values among the four groups at baseline and 3 months postoperatively.

	Control group (n=20)	**CBB group (n=20)**	**CBB+BMP-2 group (n=20)**	**CBB+BMP-2+ VEGF group (n=20)**	**P value**
Hb(mm)					
Preoperative	17.18±1.21	17.22±1.13	17.25±1.18	17.20±1.15	0.892
3 M	14.85±1.45	15.66±1.34	16.28±1.22	16.95±1.18	<0.01
Hp(mm)					
Preoperative	16.82±1.28	16.85±1.34	16.79±1.31	16.88±1.25	0.785
3 M	13.56±1.42	14.01±1.36	15.28±1.29	16.12±1.22	<0.01
W1(mm)					
Preoperative	6.35±0.72	6.37±0.76	6.42±0.68	6.39±0.74	0.915
3 M	3.98±0.78	4.43±0.67	5.12±0.65	5.68±0.58	<0.01
W2(mm)					

Preoperative	8.15±0.58	8.10±0.60	8.18±0.55	8.22±0.62	0.685
3 M	4.85±1.15	5.49±1.05	6.85±0.88	7.42±0.76	<0.01
W3(mm)					
Preoperative	10.72±0.65	10.76±0.60	10.82±0.58	10.85±0.62	0.825
3 M	8.56±0.95	9.10±0.86	9.85±0.72	10.35±0.65	<0.05
Hu(mm)					
Preoperative	1358.45±42.18	1363.72±38.21	1365.28± 41.65	1362.84±39.72	0.892
3 M	1885.32±135.68	2055.67±120.82	2285.45± 98.25	2456.78±82.35	<0.01

3.3 Postoperative Pain Assessment

Visual analogue scale (VAS) pain scores were systematically evaluated at days 1, 3, and 7 following extraction surgery, revealing significant differences between treatment groups at all time points ($p < 0.05$) (Table 4). On postoperative day 1, the CBB+BMP-2+VEGF group demonstrated significantly lower pain scores (4.6 ± 0.8) compared to the control group (6.2 ± 0.9, $p < 0.05$), with the CBB alone (5.8 ± 0.8) and CBB+BMP-2 groups (5.1 ± 0.9) showing intermediate values. This pattern persisted throughout the observation period, with day 3 scores of 2.5 ± 0.5 versus 3.8 ± 0.7 for the combination and control groups respectively ($p < 0.05$), and day 7 scores of 0.9 ± 0.7 versus 1.8 ± 1.1 ($p < 0.05$). The consistent reduction in pain intensity across all time points in the CBB+BMP-2+VEGF group suggests that this combination treatment provides superior pain management throughout the critical early healing phase, with a clear dose-dependent relationship between treatment complexity and analgesic efficacy.

Table 4. Comparison of VAS Pain Scores Among Four Groups. *CBB: Calcined bovine bone. Note: P < 0.05 indicates statistically significant differences between groups; * indicates significant difference compared to the control group.*

Group	**Visual Analogue Scale (VAS)**		
	Day 1	**Day 3**	**Day 7**
Control Group (Empty control)	6.2±0.9	3.8±0.7	1.8±1.1
CBB Group	5.8±0.8	3.4±0.6	1.5±0.9
CBB + BMP-2 Group	5.1±0.9	2.9±0.6	1.2±0.8
CBB + BMP-2 + VEGF Group	4.6±0.8*	2.5±0.5*	0.9±0.7*
P value	<0.05	<0.05	<0.05

3.4 Soft Tissue Healing Assessment

The Landry Wound Healing Index (LWHI) was used to evaluate soft tissue healing quality at 1, 2, and 3 weeks postoperatively, with scores ranging from 1 (very poor healing) to 5 (excellent healing). Significant differences between treatment groups were observed at all time points ($p < 0.05$) (Table 5). At one week, the control group demonstrated the poorest healing scores (2.3 ± 0.7), while the CBB+BMP-2+VEGF group achieved significantly superior healing (4.1 ± 0.5, $p < 0.05$), with the CBB alone (2.8 ± 0.6) and CBB+BMP-2 groups (3.5 ± 0.6, $p < 0.05$) showing intermediate improvements. By two weeks, the healing pattern remained consistent, with the combination treatment group maintaining the highest scores (4.9 ± 0.3) compared to controls (3.6 ± 0.6, $p < 0.05$). At three weeks, both the CBB+BMP-2 and CBB+BMP-2+VEGF groups achieved perfect healing scores of 5.0 ± 0.0 ($p < 0.05$), significantly outperforming the control group (4.7 ± 0.4) and CBB alone group (4.9 ± 0.3). These results demonstrate that the addition of growth factors, particularly in combination, significantly accelerates soft tissue healing and enhances wound quality throughout the early healing period, with the most pronounced benefits observed during the critical first two weeks of recovery.

Table 5. Comparison of Landry Wound Healing Index (LWHI) Among Four Groups. *P < 0.05 indicates statistically significant differences between groups; * indicates significant difference compared to the control group. CBB: Calcined bovine bone; LWHI scores range from 1 (very poor healing) to 5 (excellent healing)*

Group	Landry Wound Healing Index (LWHI)		
	1 week	2 weeks	3 weeks
Control Group (Empty control)	2.3±0.7	3.6±0.6	4.7±0.4
CBB Group	2.8±0.6	4.1±0.5	4.9±0.3
CBB + BMP-2 Group	3.5±0.6*	4.6±0.4*	5.0±0.0*
CBB + BMP-2 + VEGF Group	4.1±0.5*	4.9±0.3*	5.0±0.0*
P value	<0.05	<0.05	<0.05

3.5 Patient Satisfaction Assessment

Patient satisfaction scores were evaluated at three months post-surgery using a 10-point scale ranging from 1 (very unsatisfied) to 10 (very satisfied), revealing significant differences between treatment groups ($p < 0.05$) (Table 6). The control group recorded the lowest satisfaction scores at 7.5 ± 1.1, while the CBB+BMP-2+VEGF group achieved the highest patient satisfaction with scores of 9.2 ± 0.6, representing a statistically significant improvement compared to controls ($p < 0.05$). The CBB alone group showed modest improvement over controls with scores of 7.9 ± 1.0, while the CBB+BMP-2 group demonstrated significantly higher satisfaction levels at 8.6 ± 0.7 ($p < 0.05$). These results indicate a clear progressive improvement in patient satisfaction correlating with treatment complexity, with the combination therapy group achieving satisfaction scores approaching the maximum rating. The superior satisfaction in the growth factor-enhanced groups likely reflects the cumulative benefits of improved bone preservation, reduced postoperative pain, enhanced soft tissue healing, and overall treatment outcomes observed throughout the study period.

Table 6. Patient Satisfaction Scores at 3 Months Post-surgery. *CBB: Calcined bovine bone; Satisfaction scores range from 1 (very unsatisfied) to 10 (very satisfied). P < 0.05 indicates statistically significant differences between groups; * indicates significant difference compared to the control group.*

Group	Patient Satisfaction Score (1-10)
Control Group (Empty control)	7.5±1.1
CBB Group	7.9±1.0
CBB + BMP-2 Group	8.6±0.7*
CBB + BMP-2 + VEGF Group	9.2±0.6*
P value	<0.05

4. Discussion

This randomized controlled trial demonstrates significant advantages of growth factor combinations in socket preservation, with several key findings emerging from the comparative analysis. The CBB+BMP-2+VEGF combination group achieved superior alveolar ridge preservation compared to all other treatment modalities, showing the least dimensional loss in both height and width measurements at three months post-extraction. A clear dose-response relationship was established across all measured parameters, with treatment efficacy progressively improving from natural healing through single-agent CBB to dual combination therapy, culminating in optimal outcomes with the triple combination approach. Beyond dimensional preservation, the growth factor-enhanced treatments demonstrated superior pain management profiles, with significantly lower VAS scores throughout the early postoperative period, and accelerated soft tissue healing as evidenced by enhanced Landry wound healing scores. Patient satisfaction scores reflected these clinical improvements, with the combination therapies achieving significantly higher ratings than conventional approaches, indicating that the enhanced clinical outcomes translated into meaningful improvements in patient-reported experience and quality of life.

The superior outcomes observed with the CBB+BMP-2+VEGF combination can be attributed to the complex molecular crosstalk and synergistic mechanisms between these growth factors during bone regeneration. At the cellular level, BMP-2 and VEGF operate through complementary pathways that enhance each other's biological effects through positive feedback loops and shared signaling cascades (BMP-2 and VEGF-A modRNAs in collagen scaffold synergistically drive bone repair through osteogenic and angiogenic pathways). VEGF functions as a master regulator of angiogenesis by promoting endothelial cell migration and proliferation, while

simultaneously activating endogenous BMP-2 expression in vessel-associated mesenchymal stem cells through the Akt/β-catenin pathway [6]. Conversely, BMP-2 stimulates osteoblasts to produce VEGF in an autocrine manner, creating a self-reinforcing cycle that couples osteogenesis to angiogenesis [7]. The temporal coordination of these processes is critical, as VEGF-induced neovascularization provides the optimal microenvironment for BMP-2-mediated osteogenic differentiation by delivering essential nutrients, oxygen, and osteoprogenitor cells to the regeneration site [8]. Furthermore, the newly formed blood vessels secrete osteogenic factors such as additional BMP-2 and BMP-4, which further enhance osteoblast differentiation and mineralization [9]. This coordinated angiogenic-osteogenic coupling is mediated through the HIF-1α/VEGF axis and Notch signaling pathways, where optimal VEGF concentrations promote the development of specialized Type H endothelial phenotypes that possess pro-osteogenic angiocrine functions [10]. The synergistic interaction between BMP-2 and VEGF also enhances the recruitment and survival of both endothelial and osteogenic progenitor cells, prolonging their functional activity and ultimately resulting in superior bone preservation and soft tissue healing compared to individual growth factor applications [11].

Several limitations should be acknowledged in the interpretation of our findings. First, the relatively short follow-up period of three months may not fully capture the long-term stability and remodeling patterns of the preserved alveolar ridge, as bone maturation and integration processes continue beyond this timeframe. Second, the single-center design and specific patient population may limit the generalizability of our results to diverse ethnic groups, different geographical regions, or patients with varying systemic health conditions that could influence bone healing responses. Third, while our study demonstrated superior clinical outcomes with the CBB+BMP-2+VEGF combination, we did not investigate the optimal dosing ratios or release kinetics of these growth factors, which may significantly impact treatment efficacy and safety profiles. Fourth, the absence of histomorphometric analysis from human samples, due to ethical constraints, limited our ability to directly assess cellular-level responses and the quality of newly formed bone tissue. Fifth, our study focused exclusively on molar and premolar extractions, and the applicability of these findings to anterior teeth or more complex extraction scenarios remains unclear. Additionally, the economic cost-effectiveness analysis was not performed, which is crucial for clinical implementation and healthcare policy decisions. Finally, potential long-term complications such as heterotopic ossification, immune responses to xenogeneic materials, or growth factor-related adverse effects require extended observation periods and larger patient cohorts to adequately assess, representing important areas for future investigation.

The findings of this study provide compelling evidence for the clinical translation of growth factor-enhanced socket preservation protocols, potentially transforming current dental practice paradigms. The demonstrated superiority of the CBB+BMP-2+VEGF combination suggests that clinicians could achieve more predictable outcomes in alveolar ridge preservation, reducing the need for complex bone augmentation procedures prior to implant placement and ultimately improving treatment efficiency while reducing patient morbidity. From a healthcare economics perspective, although the initial material costs may be higher, the prevention of extensive ridge reconstruction procedures could result in significant long-term cost savings and reduced treatment time. However, successful clinical implementation will require the development of standardized protocols for growth factor preparation, storage, and application, as well as comprehensive training programs for practitioners. Future research should prioritize several key areas: first, large-scale multicenter randomized controlled trials with extended follow-up periods to validate these findings across diverse patient populations and establish long-term safety profiles; second, dose-optimization studies to determine the minimal effective concentrations of BMP-2 and VEGF that maximize therapeutic benefits while minimizing potential adverse effects; third, investigation of patient-specific factors such as genetic polymorphisms, systemic diseases, and medication use that may influence treatment outcomes, enabling the development of personalized treatment algorithms. Additionally, research into alternative delivery systems, including sustained-release matrices and bioactive coatings, could enhance the temporal control of growth factor release and improve clinical outcomes. The development of point-of-care diagnostic tools to assess individual healing capacity and predict treatment success would further advance the field toward precision medicine approaches. Finally, health economics studies evaluating cost-effectiveness ratios and quality-adjusted life years will be essential for healthcare policy decisions and insurance coverage considerations, ultimately determining the widespread adoption of these advanced regenerative therapies in routine clinical practice.

5. Conclusion

This randomized controlled clinical trial demonstrates that the combination of calcined bovine bone with BMP-2 and VEGF significantly enhances alveolar ridge preservation compared to conventional approaches or single-agent treatments. The CBB+BMP-2+VEGF group achieved superior dimensional preservation with minimal bone loss

(0.25±0.03 mm buccal height reduction vs. 2.33±0.24 mm in controls), accelerated soft tissue healing, reduced postoperative pain, and higher patient satisfaction scores. The synergistic effects of these growth factors create an optimal microenvironment that couples angiogenesis to osteogenesis, resulting in enhanced bone quality as evidenced by increased Hounsfield unit values and improved clinical outcomes. These findings establish a clear dose-response relationship across all measured parameters, with treatment efficacy progressively improving from natural healing through dual combination therapy to the triple combination approach. The results provide compelling evidence for the clinical implementation of growth factor-enhanced socket preservation protocols, potentially transforming current practice standards and improving predictability of implant site development. Future multicenter trials with extended follow-up periods and cost-effectiveness analyses will be essential to validate these promising findings and facilitate widespread clinical adoption of this innovative regenerative approach.

6. Declaration

6.1 Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The research protocol was reviewed and approved by the Medical Ethics Committee of Jiangxi Provincial People's Hospital (Ethics Approval Number: 2025 (050)). All participants provided written informed consent after receiving comprehensive information about the study objectives, procedures, potential risks, and benefits. Participants were informed of their right to withdraw from the study at any time without compromising their standard dental care.

6.2 Consent for Publication

Not applicable. This manuscript does not contain any individual person's data in any form.

6.3 Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request, subject to institutional data sharing policies and patient privacy protection requirements.

6.4 Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

YX conceived and designed the study, performed all surgical procedures, conducted the clinical assessments, analyzed and interpreted the data, and drafted the initial manuscript. RH participated in patient recruitment, assisted with surgical procedures, and contributed to data collection and radiographic measurements. SL contributed to study design, performed statistical analysis, and assisted with manuscript preparation. YL and YH participated in patient follow-up assessments, data management, and critical revision of the manuscript. GW supervised the entire study, provided clinical expertise, contributed to study design and methodology, and critically reviewed and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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