

2026

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Recommended Citation

Ye, Peng; Li, Shu; Fan, Ying-Ying; Han, Bing-Xue; and Zhu, Shan-Shan (2026) "Efficacy of concentrated growth factors preventing medication-related osteonecrosis of the jaw following tooth extraction in patients on intravenous bisphosphonates: A randomized controlled trial," *Journal of Dental Sciences*: Vol. 21: Iss. 2, Article 33.

Available at: <https://jds.ads.org.tw/journal/vol21/iss2/33>

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Original Article

Efficacy of concentrated growth factors preventing medication-related osteonecrosis of the jaw following tooth extraction in patients on intravenous bisphosphonates: A randomized controlled trial

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Received 4 August 2025; Final revision received 9 August 2025

Available online 1 April 2026

KEYWORDS

Concentrated growth factors;
Minimally invasive tooth extraction;
MRONJ;
Prevention

Abstract *Background/purpose:* Medication-related osteonecrosis of the jaw (MRONJ) constitutes a severe postoperative complication following tooth extraction in patients with intravenous bisphosphonates (BPs) exposure. This study aimed to evaluate concentrated growth factors (CGF) in preventing MRONJ and enhancing tissue healing after tooth extraction in intravenous BPs treated patients.

Materials and methods: This randomized controlled trial enrolled 119 patients (150 extraction sites). Extraction sites were randomly allocated to minimally invasive extraction alone (control, N = 75) or with CGF (test, N = 75). MRONJ incidence was assessed at least 8 weeks postoperatively. Gingival buccolingual width and fissure area were measured immediately after extraction and at 1, 2, and 4 weeks postoperatively.

Results: In the total cohort and the intravenous BPs combined with denosumab cohort, the incidence of MRONJ in the test group was significantly lower than that in the control group

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<https://doi.org/10.1016/j.jds.2025.08.021>

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($P = 0.028$ and $P = 0.022$, respectively). The test group showed significantly greater reduction in postoperative gingival buccolingual width at 1, 2 and 4 weeks and gingival fissure area at 1 and 2 weeks compared to controls ($P < 0.05$). MRONJ patients had greater intravenous BPs injection times than those without MRONJ ($P < 0.001$).

Conclusion: Minimally invasive tooth extraction with CGF may effectively reduce the risk of MRONJ and promote tissue healing in patients treated with intravenous BPs, particularly those receiving concomitant denosumab therapy.

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Introduction

Medication-related osteonecrosis of the jaw (MRONJ) has emerged as a critical complication linked to antiresorptive agent use, particularly in patients undergoing invasive dental procedures such as tooth extraction.¹ Bisphosphonates (BPs), among the most widely used antiresorptive agents, are commonly prescribed to manage conditions such as osteoporosis and various malignancies, due to their ability to inhibit osteoclast-mediated bone resorption.² MRONJ is characterized by the presence of exposed bone in the maxillofacial region for longer than 8 weeks in patients with a history of BPs therapy who have not undergone radiation therapy to the head and neck.³

Currently, strategies to prevent MRONJ in patients receiving intravenous BPs have been widely explored, yet no consensus has been reached. Recent literature suggests that adequate dental assessment, timely intervention, and meticulous postoperative care are crucial in minimizing the risk of MRONJ.⁴ Among various approaches, the application of concentrated growth factor (CGF) has gained attention for its potential to enhance tissue healing and regeneration following tooth extraction.⁵ CGF, a derivative of autologous blood, is rich in growth factors and has demonstrated promising results in promoting soft and hard tissue regeneration.⁶

This study aims to elucidate the effectiveness of CGF in preventing MRONJ and promoting tissue healing following tooth extraction in patients undergoing intravenous BPs therapy.

Materials and methods

Study design

This single-center randomized controlled trial was conducted at Beijing Hospital from December 2023 to April 2025. The study protocol was approved by the Ethical Committee of Beijing Hospital (2406-015-140) and has been registered with the Chinese Clinical Trial Registry (ChiCTR2300078023).

Participants

Eligible participants for this study were required to meet the following inclusion criteria: (1) a history of, or current

treatment with, intravenous BPs (pamidronate disodium, zoledronic acid, ibandronate sodium, clodronate disodium, etidronate disodium or tiludronate disodium, etc.); (2) good systemic health, defined as American Society of Anesthesiologist physical status classification I or II; (3) presence of teeth deemed unsalvageable; (4) completion of periodontal treatment; and (5) voluntary willingness to participate in the study and sign informed consent.

The exclusion criteria included: (1) current smokers; (2) pregnancy; (3) individuals with a history of head and neck radiation therapy; (4) current user of immunosuppressants; (5) presence of acute infection; and (6) existing signs of MRONJ prior to tooth extraction.

All patients provided written informed consent before enrollment in the study.

Randomization and masking

Randomization was performed via SPSS-generated block randomization to ensure equal group allocation, with assignment schemes concealed in opaque coded envelopes. Each extraction site was sequentially randomized to the test or control group. Postoperatively, a blinded observer measured gingival buccolingual width, gingival fissure area, and monitored MRONJ occurrence at prespecified time points.

Procedures

In the test group, 10 ml of venous blood was collected from the antecubital vein pre-extraction and centrifuged to prepare CGF using a centrifuge (Medifuge MF200; Silfrudent, Santa Sofia, Italy). Minimally invasive extraction was performed, with the alveolar ridge highest point maintained at least 2 mm subgingival to reduce bone exposure risk. Post-extraction, CGF was compressed into a thick membrane to fully cover the fresh socket, overlaid with a collagen sponge, and the gingiva was approximated and sutured (Fig. 1).

In contrast, for patients in the control group, a minimally invasive tooth extraction was performed (one tooth extracted per procedure), after which the fresh socket was directly covered with a collagen sponge, followed by gingival approximation and suturing.

All patients were monitored at 1 week, 2 weeks, 4 weeks, 8 weeks and 3 months (or more) postoperatively for follow-up.

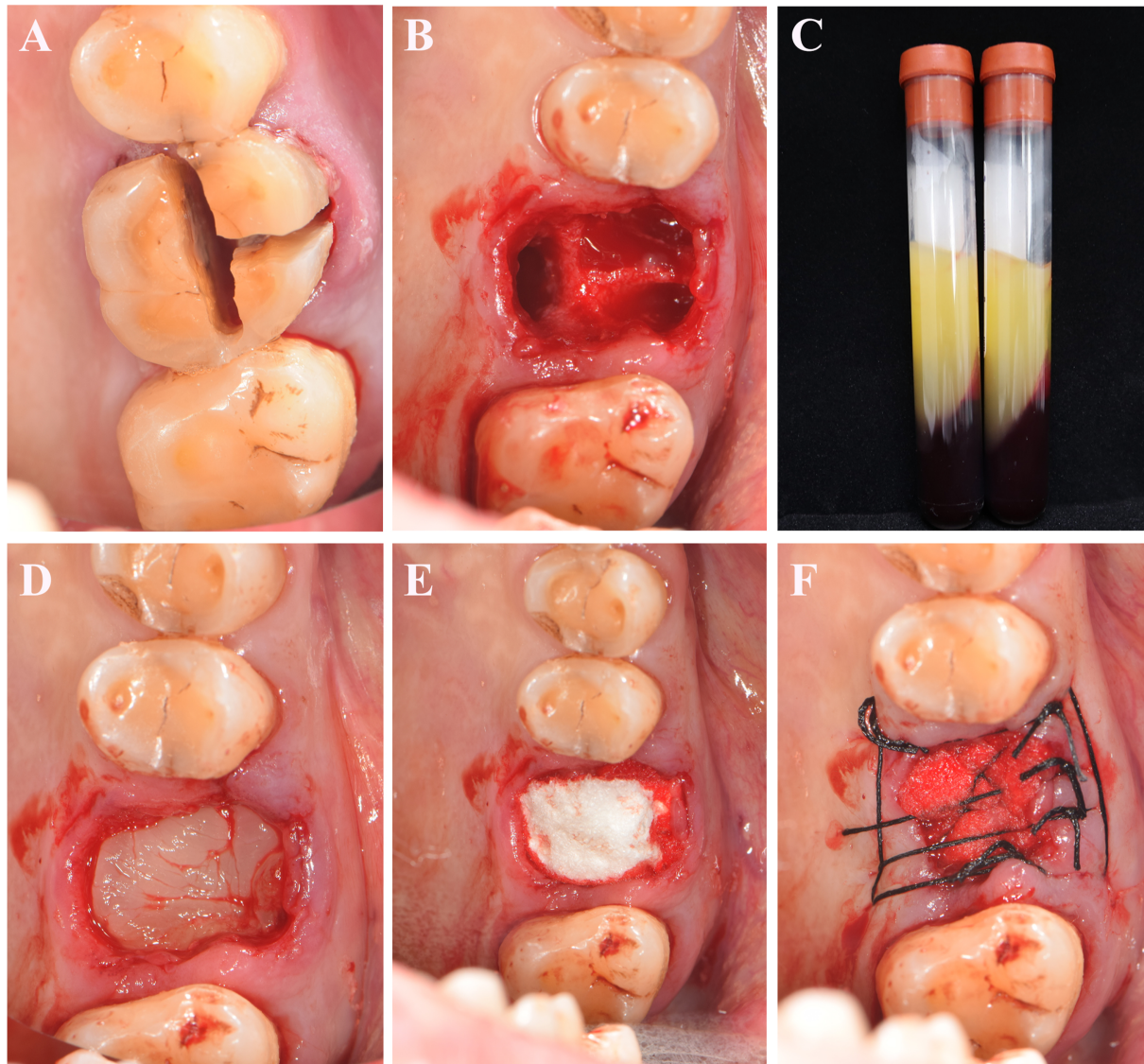


Figure 1 Step-by-step illustration of operative procedure in the test group. Extracting the maxillary first molar using a minimally invasive technique (A), Post-extraction socket with the alveolar ridge crest positioned at least 2 mm below the gingival margin (B), Prepared Concentrated Growth Factors (CGF) in centrifuge tubes (C), Application of CGF to cover the whole socket walls (D), Placement of a collagen sponge over the CGF for protection (E), Appropriating and suturing of the gingival fissure (F).

Outcomes

The primary efficacy outcome was the incidence of MRONJ. The diagnosis of MRONJ encompasses three key components: 1) Current or prior exposure to antiresorptive agents, or in conjunction with immune modulators or antiangiogenic drugs. 2) Exposed bone or bone accessible via intraoral/extraoral fistulae in the maxillofacial area, with persistence exceeding 8 weeks. 3) Absence of a history of radiation therapy to the head and neck region.

The secondary efficacy outcome was gingival buccolingual width, assessed at five time points: immediately post-extraction, and at 1 week, 2 weeks, 4 weeks, and 8 weeks thereafter. Measurements were performed using a millimeter transparent ruler from the occlusal view, specifically measuring the linear distance from the midpoint of the

buccal and lingual gingival margins at the extraction site (Fig. 2A).

The third efficacy outcome was the gingival fissure area. Measurements were conducted using a millimeter transparent ruler to determine the area of the gingival fissure at the top of the extraction socket from the occlusal view (Fig. 2B). Any areal measuring less than half a square unit was disregarded, while those between half a square and one square unit were recorded as one full unit.

Study power

Sample size was determined based on the latest literature evaluating the efficacy of autologous platelet rich concentrates in preventing MRONJ following tooth extraction,

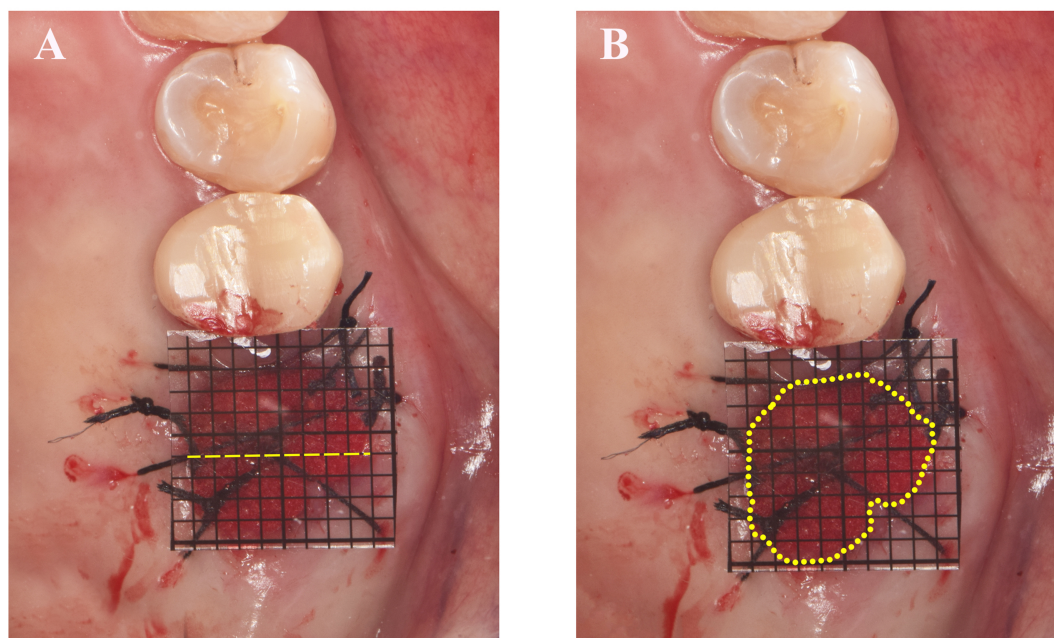


Figure 2 Measuring the buccolingual gingival width and fissure area at the top of the extraction socket from the occlusal view. The yellow straight dashed line measuring the linear distance between the midpoints of buccal and lingual gingival margin (A). The yellow dashed irregular circle measuring the area of the gingival fissure (B).

wherein the incidence of MRONJ in the test group was 0 %, while the control group was 12.2 % (at tooth level).⁷ With a type I error of 0.05 and a study power of 80 %, the minimum sample size was calculated as 112 (56 extractions in each group). Considering the inevitable dropout and indefinite availability of subjects, the final sample size was decided to be 150 (75 extractions in each group).

Statistical analysis

All statistical analyses were performed using SPSS (version 23.0; IBM, Armonk, NY, USA). Categorical variables were reported as frequencies and percentages; continuous data were summarized as means \pm standard deviations, with normality assessed via the Shapiro–Wilk test. Group differences in baseline demographics, clinical characteristics, MRONJ incidence, and other variables were analyzed using the Chi-square test, Fisher’s exact test, independent samples *t*-test, or Mann–Whitney U test. A *P* value $<$ 0.05 was considered statistically significant.

Results

Participants

A total of 136 participants were screened between December 2023 and April 2025, among whom 9 declined participation prior to treatment initiation. During the experiment, 8 female participants were excluded: 6 due to loss to follow-up and 2 owing to postoperative inflammation. Ultimately, a total of 150 extractions were performed in 119 patients completing the prespecified follow-up. Of those, 75 extractions were randomly assigned to the test group and 75 to the control group. In general, the baseline

demographic and clinical characteristics were balanced between the two groups (Table 1).

MRONJ incidence

All patients were followed up for at least 3 months. In the test group, all extraction sockets underwent full mucosal coverage without alveolar bone exposure or gingival fistula at the last follow-up. In the control group, MRONJ sign was detected at 6 extraction sites (6 patients, 1 male and 5 females) on follow-up (\geq 8 weeks). One of them was being treated for multiple bone metastatic malignancies with Zoledronic Acid (5 mg per dose) once a month for half a year. Another one was previously treated with Zoledronic Acid (5 mg per dose) for 6 times and denosumab (60 mg per dose) for 5 times for osteoporosis, and ever treated with prednisone (low-dose) for mycotic pneumonia. The remaining four patients had previously received zoledronic acid therapy 4–7 times and denosumab (60 mg per dose) 2–4 times for osteoporosis management. Five of these MRONJ cases were classified as stage 1 and one as stage 2. All these six patients subsequently underwent local debridement and local mucoperiosteal primary closure. Fortunately, all these MRONJ cases recovered uneventfully on the next 8 weeks follow-up.

In comparison, the MRONJ incidence in the control group (8 %) was significantly higher than that in the test group (0) ($P = 0.028$) (Table 2). Subgroup analyses revealed that in the cohort receiving intravenous BPs combined with denosumab, the test group showed a significantly lower MRONJ incidence (0 in 24) than the control group (5 in 23) ($P = 0.022$). While, in the cohort receiving intravenous BPs alone, the incidence of MRONJ in the test group (0 in 51) was comparable to that in the control group (1 in 52) ($P = 1.000$).

Table 1 Baseline demographics and clinical characteristics.

Variables	Test group	Control group	P-value
	n* = 75	n* = 75	
Gender			
Female	72	73	1.000 ^a
Male	3	2	
Age (yr)			
Mean	69.43	69.09	0.817 ^b
SD	9.40	8.12	
Body weight (kg)			
Mean	61.96	60.77	0.701 ^c
SD	13.80	9.96	
Body height (cm)			
Mean	160.25	159.84	0.218 ^c
SD	12.28	5.80	
Diabetes			
Yes	12	10	0.644 ^d
No	63	65	
Bps use duration (mth)			
Mean	25.51	22.67	0.928 ^c
SD	24.50	16.26	
Bps injection times			
Mean	3.09	3.07	0.998 ^c
SD	1.95	1.83	
Bps drug holiday (mth)			
Mean	50.09	49.71	0.875 ^c
SD	43.25	42.20	
Reason for using iv-BPs			
Osteoporosis	2	3	1.000 ^a
Malignancy	73	72	
Concomitant denosumab			
iv-BPs alone	51	52	1.000 ^d
iv-BPs + denosumab	24	23	
Ever glucocorticoid			
Yes	2	3	1.000 ^a
No	73	72	

n*: at tooth level.

SD: standard deviation; iv-BPs: intravenous bisphosphonates.

^a Fisher's exact test.

^b Independent *t*-test.

^c Mann–Whitney U test.

^d Pearson Chi-square test.

Gingival buccolingual width

The reduction in gingival buccolingual width in the control group at 1 week, 2 weeks, and 4 weeks postoperatively was measured at 0.91 ± 1.29 mm, 1.87 ± 1.93 mm, and 3.55 ± 2.26 mm, respectively. These values were significantly less than those observed in the test group, which exhibited reductions of 2.05 ± 1.74 mm, 2.97 ± 1.87 mm, and 4.47 ± 2.23 mm at the same time points ($P < 0.001$, $P = 0.019$) (Table 2).

Gingival fissure area

The reduction in the gingival fissure area in the test group at 1 week and 2 weeks postoperatively was

17.24 ± 15.68 mm² and 22.11 ± 16.76 mm², respectively. These reductions were significantly greater than those recorded in the control group, which showed reductions of 7.16 ± 8.27 mm² and 14.27 ± 14.04 mm² at the same time points (all $P < 0.001$). However, at the 4-weeks post-operative mark, no significant difference was observed between the control group (27.96 ± 19.42 mm²) and the test group (25.88 ± 19.49 mm²) ($P = 0.488$) (Table 2).

BPs injection times and drug holiday

There was a significant difference in BPs injection times between the MRONJ patients (5.50 ± 1.05 times) and the non-MRONJ patients (2.98 ± 1.85 times) ($P < 0.001$). However, no significant difference was noted in drug holiday time between the MRONJ patients (27.67 ± 25.72

Table 2 Comparison of variables between test and control groups in the total cohort.

Variables	Test group	Control group	P-value
	n* = 75	n* = 75	
MRONJ			
Yes	0	6	0.028 ^a
No	75	69	
Gingival fissure width reduction (mm)			
1 week post-op	2.05 ± 1.74	0.91 ± 1.29	<0.001 ^b
2 weeks post-op	2.97 ± 1.87	1.87 ± 1.93	<0.001 ^b
4 weeks post-op	4.47 ± 2.23	3.55 ± 2.26	0.019 ^b
Gingival fissure area reduction (mm ²)			
1 week post-op	17.24 ± 15.68	7.16 ± 8.27	<0.001 ^b
2 weeks post-op	22.11 ± 16.76	14.27 ± 14.04	0.002 ^b
4 weeks post-op	27.96 ± 19.42	25.88 ± 19.49	0.488 ^b

n*: at tooth level.

^a Fisher's exact test.

^b Mann–Whitney U test.

months) and the non-MRONJ patients (50.83 ± 42.95 months) (*P* = 0.166) (Table 3).

Discussion

In this trial, we found the incidence of MRONJ was significantly lower in the test group across the total cohort, particularly in patients receiving intravenous BPs combined with denosumab. This suggests CGF may play a vital role in preventing MRONJ in these population. Similar findings have been reported by Besi et al. in their observational study, wherein they noted a reduction in the incidence of BRONJ through the use of platelet-rich fibrin (PRF).⁷ Del Fabbro et al. also noted the use of PRF in extraction sites of patients on zoledronic acid therapy mitigated BRONJ occurrences.⁸ However, most such studies use retrospective designs or small samples, limiting evidence strength.

Additionally, while several previous researches suggested the preparation of local mucoperiosteal flaps during extraction may be necessary for these patients,^{9–12} all subjects in our study underwent minimally invasive extractions without local flaps. Instead, we employed CGF to fill the extraction socket and approximate the buccolingual gingival tissues, a strategy that not only contributed to MRONJ prevention but also mitigated surgical trauma. This might be attributed to CGF's ability to prevent early bone

exposure and its rich content of various growth factors that facilitate soft tissue healing, consequently reducing the opportunity for bone exposure. Our findings support this hypothesis, as we recorded significantly greater reductions in gingival wound width and area at 1 and 2 weeks post-operatively in the experimental group compared to the control group, indicating an accelerated epithelialization process and a notable decrease in the risk of bone exposure. Compared to earlier generation autologous platelet concentrates, CGF offers higher concentrations and more uniform distributions of growth factors, a denser fibrin matrix, and a longer degradation time, potentially providing superior effects in promoting tissue healing and exerting anti-inflammatory properties.^{13,14}

In our study, the MRONJ incidence of control group was 8 % in the total cohort. This rate can be contextualized through comparison with existing literature. Besi et al. reported a 12.2 % MRONJ rate (5/41 extractions) in non-PRF controls receiving anti-resorptive/anti-angiogenic agents, a figure likely inflated by their large proportion of malignancy patients and non-randomized design.⁷ Bodem et al. noted a 13.1 % MRONJ incidence following extraction in patients receiving intravenous BPs.¹⁵ However, their study lacks the control group limiting the generalizability. Coropciuc et al. reported a 2.7 % per-person-year MRONJ incidence in osteoporotic patients on antiresorptive agents, though 36.5 % of their cohort received low-risk oral alendronate.¹⁶

Table 3 Comparative assessment of variables among MRONJ and non-MRONJ groups.

Variables	MRONJ group	non-MRONJ group	P-value
	n* = 6	n* = 144	
iv-Bps injection times	5.50 ± 1.05	2.98 ± 1.85	<0.001 ^a
iv-Bps drug holiday (mth)	27.67 ± 25.72	50.83 ± 42.95	0.166 ^a

n*: at tooth level.

MRONJ: medication-related osteonecrosis of the jaw; iv-BPs: intravenous bisphosphonates.

^a Mann–Whitney U test.

Notably, among their 31 non-PRF cases, 25.8 % (8/31) developed MRONJ, far exceeding our 8 %.

Furthermore, our study demonstrated that MRONJ patients had received significantly more intravenous BPs than non-MRONJ counterparts. This trend confirms a dose–response relationship: higher injection frequency and cumulative dosage of intravenous BPs correlate with elevated post-extraction MRONJ risk, consistent with extensive prior research.^{17–20} Thus, dentists should implement targeted preventive measures during tooth extraction as intravenous BPs exposure increases, to mitigate MRONJ risk.

However, our investigation found no difference in drug holiday duration between MRONJ and non-MRONJ patients. This possibly imply that merely extending the drug holiday time for patients receiving intravenous BPs may not reduce the risk of MRONJ following tooth extractions. Given the scarcity of high-level evidence on this issue, the American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaw in 2022 highlighted a lack of consensus among working groups regarding the necessity of drug holidays for patients using anti-resorptive medication.¹ A potential reason for this scenario may lie in the long half-life of intravenous BPs, which can be up to 10 years.^{21,22} Theoretically, only through prolonged observation of drug holidays exceeding ten years could we determine if this practice minimizes MRONJ risk.

Denosumab, an antiresorptive agent, independently confers susceptibility to MRONJ, with numerous prior studies documenting a significant elevation in MRONJ risk when administered concomitantly with intravenous BPs.^{23–28} To mitigate denosumab's influence on our results, distribution of patients receiving intravenous BPs alone versus in combination with denosumab was balanced between test and control groups through random grouping in our study. Our subgroup analyses revealed that in the intravenous BPs combined with denosumab cohort, test group CGF application significantly reduced MRONJ incidence versus controls. This indicates that in this relatively high-risk population, CGF may prevent the occurrence of MRONJ after tooth extraction. In contrast, no significant between-group difference in MRONJ incidence was noted in the intravenous BPs alone cohort. This discrepancy may stem from that most of our included patients on intravenous BPs alone were low-risk individuals, with relatively low administration frequency and total dosage of intravenous BPs. Given these, dentists should exercise heightened vigilance to minimize MRONJ risk in this vulnerable population on concurrent therapy.²⁴

This study has several limitations. First, the inclusion of relatively few patients receiving BPs for malignancy limits our ability to conclusively demonstrate the efficacy of CGF in preventing MRONJ in this high-risk population. Thus, additional randomized controlled trials focusing specifically on this subgroup are warranted to validate the benefits of CGF. Second, some patients receiving intravenous BPs were concurrently administered denosumab, which may have introduced confounding when analyzing MRONJ risk factors.

Our findings suggest that minimally invasive tooth extraction with CGF may effectively reduce the risk of MRONJ and promote tissue healing in patients treated with

intravenous BPs, particularly in those receiving concomitant denosumab therapy.

Declaration of competing interest

The authors declare no conflicts of interest with this study, financial or otherwise.

Acknowledgments

The authors acknowledge the support of the National High Level Hospital Clinical Research Funding (BJ-2023-186), the Capital's Funds for Health Improvement and Research (CFH 2024-1-4101), and the National Key Research and Development Program of China (2020YFC2009005-04).

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