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Effects of Multiple Metaphyseal Hole Creation on Long Bone Growth in a Rabbit Model

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Purpose: Long bone overgrowth after pediatric skeletal injury or surgery is well recognized, whereas growth suppression without physeal injury is rare. This study aimed to evaluate the effects of creating multiple metaphyseal holes on bone growth and elucidate the underlying mechanisms in a rabbit model.

Materials and Methods: Single and dual metaphyseal holes were created in the left tibiae of immature rabbits and filled with bone wax. In the one-hole group, a hole was drilled 10 mm below the physis. In the two-hole group, an additional hole was made 5 mm below the first. Rabbits were assigned to sham (n=8), one-hole (n=8), and two-hole (n=8) groups. Tibial lengths were measured radiographically. Histologic evaluation and CD31 immunofluorescence were used to assess new bone formation and angiogenesis. Growth change was calculated as the percentage difference between the operated and contralateral limbs.

Results: The one-hole group showed significantly greater overgrowth than the sham group (1.041±1.022 mm vs. 0.027±0.342 mm, p=0.021), while the two-hole group demonstrated significant growth suppression (-0.988±0.484 mm vs. 0.027±0.342 mm, p<0.001). Histologic analysis revealed increased new bone in the one-hole group and decreased new bone formation in the two-hole group. CD31 expression was reduced in the two-hole group, indicating impaired angiogenesis.

Conclusion: A single metaphyseal hole promotes overgrowth, whereas an additional hole suppresses growth, likely through vascular disruption. These findings provide insights into bone growth regulation and its underlying mechanisms.

Key Words: Bone growth, tibia, metaphysis, angiogenesis, physis, rabbits

INTRODUCTION

In skeletally immature individuals, long bone growth can be influenced by various factors, leading to overgrowth or undergrowth during the growth period. Overgrowth has been widely reported following femoral shaft fractures, proximal tibial metaphyseal fractures, and anterior cruciate ligament reconstruction.[1-5] Various animal studies have investigated the mechanisms of overgrowth, demonstrating similar findings in experimental models. Overgrowth has been observed following periosteal stripping, metaphyseal hole creation, and cortical bone fractures.[6-10] These studies suggest that increased blood flow, microinstability, and periosteal disruption near the growth plate may contribute to excessive bone growth. Clinically, periosteal stripping or division has been utilized to induce controlled overgrowth, offering potential therapeutic applications for the correction of leg length discrepancy (LLD).[11,12]

In contrast, the undergrowth of long bones is predominantly associated with direct physeal injury.[13-15] Growth disturbances

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following physeal damage often result in the formation of a physeal bar, leading to asymmetric growth inhibition. However, cases of undergrowth without direct physeal injury have also been reported under specific conditions, such as hypervitaminosis A, isotretinoin treatment, and certain surgical interventions for femoral shaft fractures.[1,2,16-18] Isotretinoin, which is widely used for neuroblastoma and dermatologic conditions, is known to cause premature epiphyseal arrest and other skeletal abnormalities. Similarly, femoral shaft fractures, typically associated with overgrowth, may have reduced overgrowth when treated with surgical stabilization methods, such as minimally invasive plate osteosynthesis or elastic stable intramedullary nailing, potentially preventing angular deformity or LLD.[1,2,19] The reduction of overgrowth in such cases suggests that factors beyond direct physeal injury, such as alterations in vascular supply or mechanical stability, may contribute to bone growth inhibition.

We hypothesized that moderate metaphyseal stimulation induces overgrowth, whereas excessive mechanical or biological disruption leads to undergrowth. This study aimed to investigate the effects of multiple metaphyseal holes on long bone growth and elucidate the underlying pathophysiology.

MATERIALS AND METHODS

Study design

We selected 7–8-week-old male New Zealand White rabbits. All animal experimental protocols were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Yonsei University College of Medicine (IACUC No. 2023-0095), and all procedures were conducted in accordance with the ARRIVE guidelines and relevant regulations. All rabbits were acclimated in an animal care facility for an average of 14 days, were approved for use by the veterinarian, and underwent designated surgical procedures. Twenty-one New Zealand White rabbits (male, 2–2.5 kg) were obtained from commercial suppliers.

Single and dual metaphyseal holes filled with bone wax were created in the tibiae of skeletally immature rabbits (n=8 per group). Eight additional rabbits were included as sham controls and used for age-matched comparisons. In total, 24 rabbits were randomly allocated.

Surgical procedures

A longitudinal medial skin incision approximately 1.5 cm long was made over the left proximal tibial region for each procedure. The muscles were elevated off the tibia to ensure minimal disturbance to the periosteum. In the sham control group, the procedure was performed in the same manner, without hole creation. In the one-hole group, the hole was made using a Steinmann pin 10 mm below the physis under fluoroscopic guidance.[10] In the two-hole group, two-holes were drilled using a Steinmann pin 10 mm and 15 mm below the physis. The vacant space in the metaphysis below the physis was filled with bone wax. Tibiae were collected 6 weeks after the index surgery.

Radiographic analysis

Radiographic analysis was performed to measure tibial lengths using a high-resolution REX 650R X-ray system (Listem, Wonju, Korea) and CS-7 software (V1.10R00_026, Konica Minolta, Tokyo, Japan). The soft tissues surrounding the bone were removed after harvesting, and radiographs were obtained in an optimal position (Fig. 1). Tibial length was defined as the distance along the medial cortex between the proximal and distal physes, and was measured on both the operated and contralateral sides. Measurements were performed blindly to minimize subjective bias. The absolute and percentage differences in tibial lengths between the operated and contralateral limbs were calculated. Overgrowth length was determined by subtracting the length of the contralateral limb from that of the operated limb. Growth change rate, or percent increase over control, was defined as the difference in tibia length between the operated and contralateral limbs divided by the contralateral limb's tibia length, and multiplied by 100. The growth change rates between the groups were compared using percentage points.

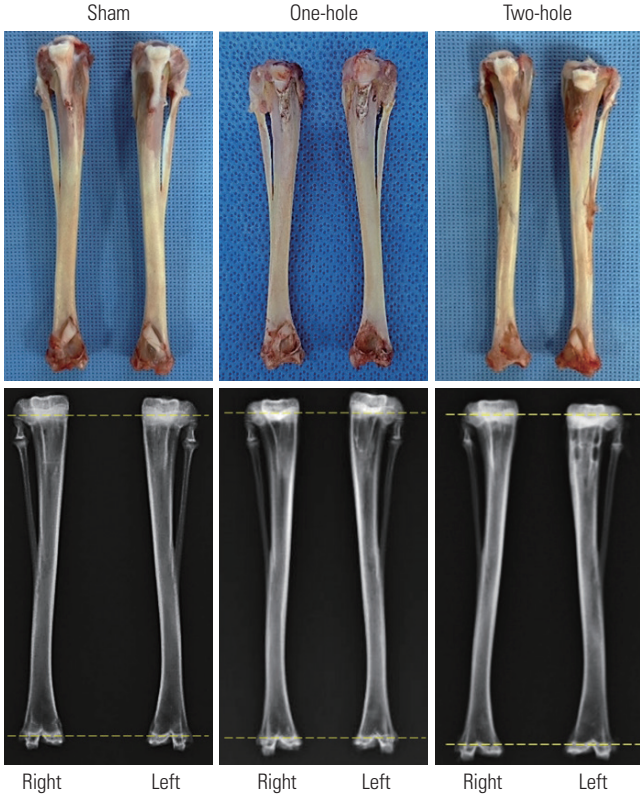

Fig. 1. Radiographic images of rabbit tibiae at 6 weeks postoperatively. Representative radiographs of the left tibiae from the sham, one-hole, and two-hole groups.

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Histologic analysis

The collected tibiae were fixed in a 3.7% paraformaldehyde solution at room temperature for 1 week and embedded in a plastic resin block. Coronal sections (50±5 μm thick) were obtained using a grinding system (EXAKT 400CS, Kulzer, Norderstedt, Germany). The samples were extracted from the resin block and decalcified in 0.5 M ethylenediaminetetraacetic acid for 4 weeks. After embedding in paraffin wax, 5-μm-thick sections were cut in the coronal plane using a rotary microtome. The sections were sequentially stained with hematoxylin and eosin (H&E). New bone length (composed of the calcified cartilage matrix) was measured as the distance from the hypertrophic zone to the trabecular bone. The length of overgrowth of new bone was calculated by subtracting the length of the contralateral limb from that of the operated limb.

The angiogenic activity of the overgrown bone area was evaluated using immunofluorescence analysis. After deparaffinization and rehydration, the paraffin sections were incubated overnight with anti-CD31 antibody (1:100; ab28364, Abcam Inc., Waltham, MA, USA). Nuclei were stained using UltraCruz aqueous mounting medium with DAPI (sc-24941, Santa Cruz, CA, USA). Fluorescence imaging was performed using an IX71 fluorescence microscope (Olympus, Tokyo, Japan).

Statistical analysis

Statistical analyses were performed using SPSS version 23 software (IBM Corp., Armonk, NY, USA). A paired t-test was used to compare tibial lengths between the operated and non-operated sides. An independent t-test was used to compare tibial overgrowth, growth change rate, and new bone overgrowth between the groups. Statistical significance was set at $p<0.05$.

RESULTS

In the sham control group, there was no significant difference in tibial length between the operated limb (103.832±3.304 mm) and the contralateral control limb (103.804±3.321 mm, $p=0.742$). In the one-hole group, the operated limb was significantly longer than the control limb (102.398±3.612 mm vs. 101.357±3.717 mm, $p=0.016$). In contrast, in the two-hole group, the operated limb was significantly shorter than the control limb (100.896±3.565 mm vs. 101.884±3.494 mm, $p=0.008$).

Growth was accelerated in the one-hole group compared to the sham group by an average of 1.014 mm (1.041±1.022 mm vs. 0.027±0.342 mm, $p=0.021$). Conversely, growth was suppressed in the two-hole group compared to the sham group by an average of 1.015 mm (-0.988±0.484 mm vs. 0.027±0.342 mm, $p<0.001$). The two-hole group exhibited 2.029 mm undergrowth on average compared to the one-hole group (-0.988±0.484 mm vs. 1.041±1.022 mm, $p<0.001$) (Fig. 2A).

Tibial length on the operated side was 0.03% greater than that of the right-sided control in the sham group, and 1.04% greater in the one-hole group. In contrast, the tibial length on the operated side was 0.97% shorter in the two-hole group than that in the right-sided control group. Bone growth rate was significantly higher in the one-hole group than that in the sham group ($p=0.021$). The two-hole group exhibited significantly less growth than the sham ($p=0.001$) and one-hole ($p<0.001$) cohorts (Fig. 2B).

By H&E staining, new bone growth was significantly increased in the one-hole group compared to the sham group (58.63±30.19 μm vs. -13.63±38.52 μm, $p=0.001$). However, new bone growth was significantly suppressed in the two-hole group compared to the sham group (-39.94±13.20 μm vs. -13.63±38.52 μm, $p=0.048$) (Fig. 3). None of the groups exhibited phy-

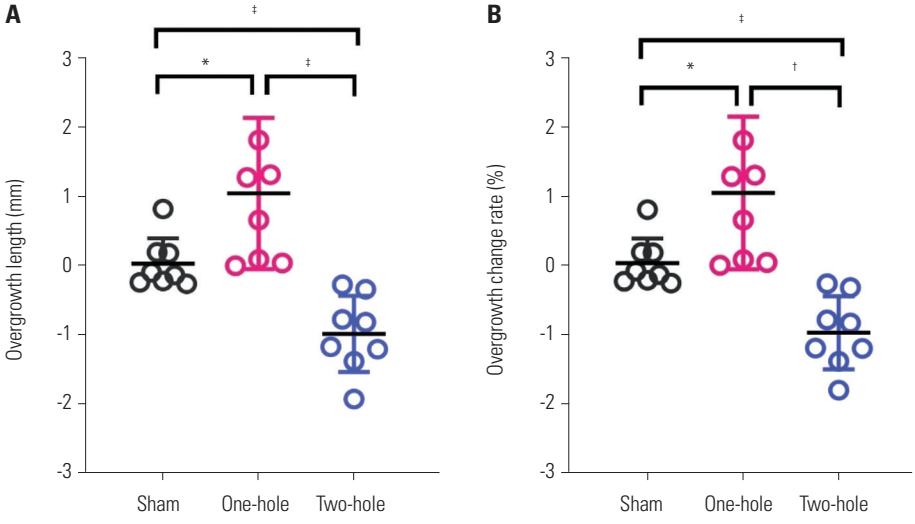

Fig. 2. Tibial overgrowth and growth change rate across different groups. (A) Quantification of tibial overgrowth based on radiographic measurements at 6 weeks postoperatively. Growth was significantly increased in the one-hole group and suppressed in the two-hole group compared to the sham group ($p<0.05$). (B) Growth change rate (%) relative to the contralateral limb. The one-hole group exhibited a higher growth change rate, whereas the two-hole group showed a significant reduction in tibial length ($p<0.05$). *$p<0.05$, †$p<0.01$, ‡$p<0.001$ between groups.

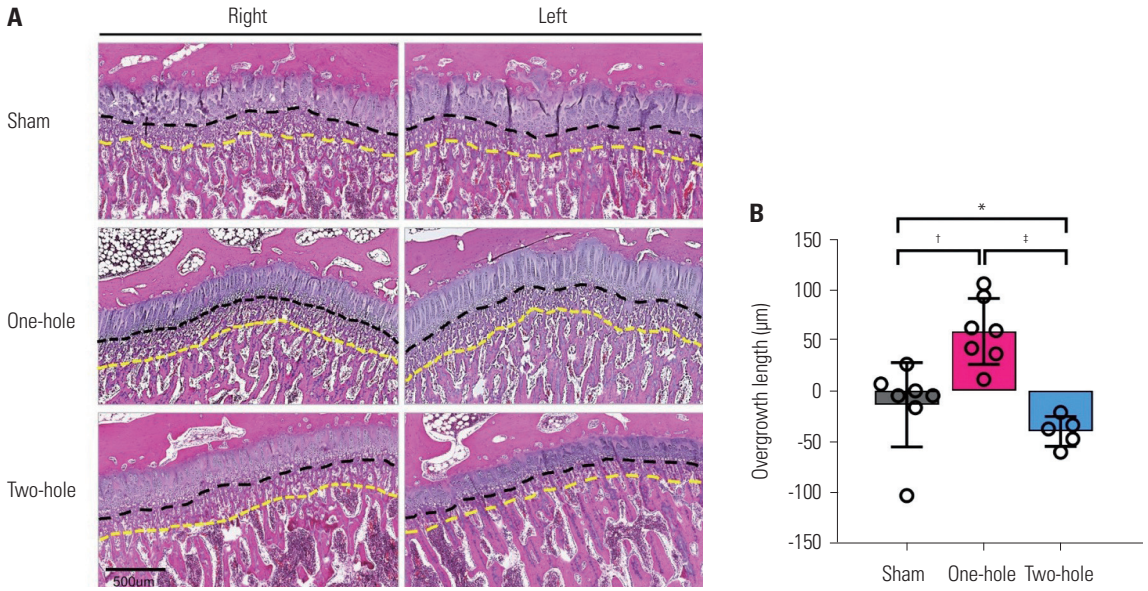

Fig. 3. Histologic analysis of new bone formation. (A) Hematoxylin and eosin staining of coronal tibial sections from each group. Yellow and black dotted lines indicate the hypertrophic zone and the new bone formation area, respectively. (B) Quantification of new bone length. The one-hole group exhibited significantly greater new bone formation than the sham group, whereas the two-hole group had significantly reduced new bone growth ($p<0.05$). *$p<0.05$, †$p<0.01$, ‡$p<0.001$ between groups.

Table 1. Comparison of Tibial Overgrowth, Growth Rate Change, and New Bone Overgrowth Length in the Two-Hole Group

Variable	Two-hole	One-hole	*p*	Sham	*p*
Overgrowth of tibia (mm)	-0.988±0.484	1.041±1.022	<0.001	0.027±0.342	<0.001
Growth change rate (%)	-0.973±0.492	1.036±1.026	<0.001	0.027±0.333	0.001
Overgrowth length of new bone (μm)	-39.94±13.20	58.63±30.19	0.003	-13.63±38.52	0.048

Values are presented as mean±standard deviation. *p*-values were calculated using independent t-tests between groups with the two-hole group as the reference.

seal bar formation or evidence of physis injury. The inhibition of the growth in the two-hole group, compared with the one-hole and sham groups, as measured by radiographic and histological analyses, is presented in Table 1.

H&E staining and fluorescence microscopy were performed to examine the capillary network around the physis. H&E staining revealed fewer capillaries in the two-hole group than in the one-hole or sham groups. Fluorescence microscopy revealed that the expression of CD31, an indicator of angiogenic activity, was significantly lower in the two-hole group than in the other two cohorts (Fig. 4).

DISCUSSION

In this study, we investigated the effects of multiple metaphyseal holes on long bone growth using a rabbit model. Our findings demonstrate that a single metaphyseal hole filled with bone wax significantly stimulated tibial overgrowth, whereas an additional hole made simultaneously led to significant growth suppression. These changes were confirmed using radiographic measurements, histological evaluation, and angiogenic analysis. Notably, CD31 expression was significantly reduced in the two-hole group, suggesting that metaphyseal vascular disruption, rather than direct physeal damage, may play a pivotal role in growth inhibition.

The phenomenon of long bone overgrowth following trauma or surgery has been well documented, particularly in pediatric femoral fractures, tibial metaphyseal fractures, and anterior cruciate ligament reconstruction.[1-5] Various animal models have replicated this effect, implicating increased blood flow, microinstability, and periosteal disruption as potential mechanisms.[6-9] Consistent with these findings, our study showed that a single metaphyseal hole induced overgrowth, possibly through local vascular stimulation and periosteal remodeling.

However, unlike previous studies that focused solely on overgrowth, our findings highlight a novel growth-suppressive effect of multiple metaphyseal holes. In clinical settings, growth suppression is typically associated with direct physeal injury, leading to physeal bar formation and growth arrest.[13-15] However, our study provides evidence that growth suppression can occur even without direct physeal damage, suggesting an alternative mechanism related to vascular disruption and reduced angiogenesis.

Our histological and immunofluorescence analyses provided insights into the mechanisms underlying growth inhibition in the two-hole group. We observed a significant reduction in CD31 expression, a key marker of angiogenesis and vascular in-

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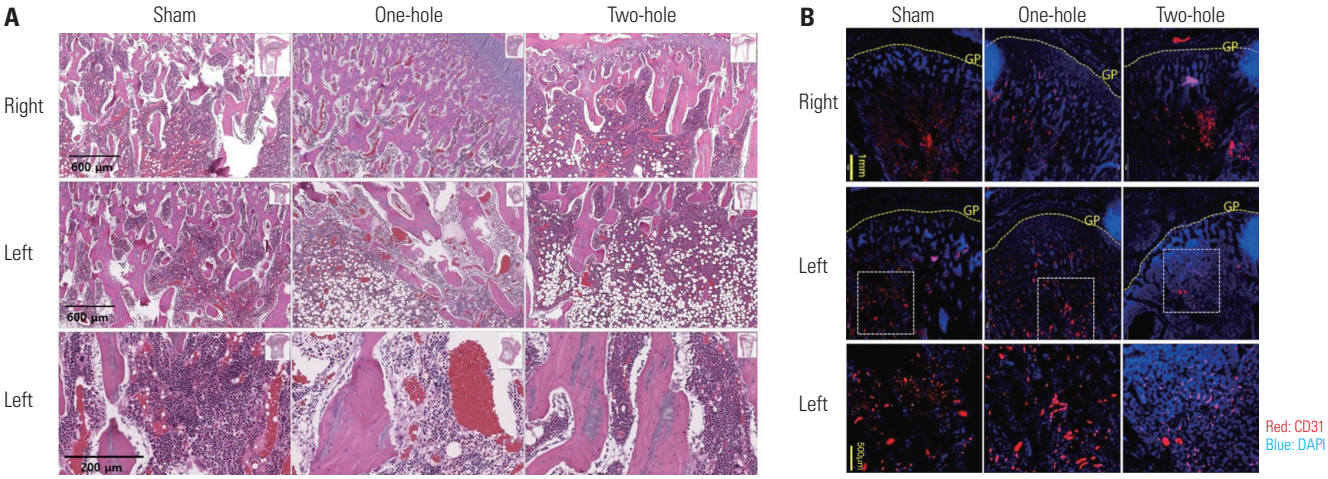

Fig. 4. Angiogenic analysis of metaphyseal vascularization. (A) Hematoxylin and eosin staining showing capillary structures in the metaphyseal region. The two-hole group displayed fewer capillaries than the one-hole and sham groups. (B) CD31 immunofluorescence analysis of angiogenesis. Sections were stained with anti-CD31 antibody (red) and 4′,6-diamidino-2-phenylindole (DAPI) (blue) to visualize endothelial cells and nuclei, respectively. The two-hole group exhibited reduced CD31 expression, indicating impaired angiogenesis. GP, growth plate.

tegrity. Previous studies have highlighted the role of type H vessels, which are characterized by high CD31 and endomucin expression, and are crucial for bone growth and remodeling.[20,21] These vessels are responsible for supplying oxygen and nutrients to the metaphysis, and their disruption may contribute to impaired endochondral ossification and subsequent growth suppression.

The absence of physeal bar formation in the histological analysis indicated that growth inhibition was not due to direct physeal injury. However, our findings suggest that vascular insufficiency in the metaphysis plays a critical role in restricting bone elongation. Multiple perforations may have disrupted the local vascular network, leading to a decreased blood supply and reduced angiogenic signaling around the physis. This mechanism aligns with previous research demonstrating that bone growth is closely associated with vascularization, and that disruptions in blood supply can impair osteogenesis and potentially affect endochondral bone formation.[21]

Our findings have important clinical implications for growth modulation strategies in pediatric orthopedic surgery. Periosteal stripping and controlled injury have been used to induce overgrowth for leg-length discrepancy correction.[11,12] Our study suggests that high vascular disruption at the metaphysis may lead to unintended growth suppression, even in the absence of direct physeal injury. This underscores the importance of preserving metaphyseal vascular integrity during surgical interventions involving drilling, curettage, or hardware placement near the growth plate.

Current treatments for growth inhibition, such as epiphysiodesis or guided growth techniques, primarily target the physis. However, our results indicate that manipulating metaphyseal vascularization may serve as an alternative approach for modulating bone growth. The observed reduction in CD31 expression in the two-hole group suggests that targeting angiogenesis could be explored as a therapeutic strategy for growth modulation. Future research should investigate whether pharmacological or surgical approaches to enhance the metaphyseal blood supply could mitigate growth suppression in clinical settings. Additionally, these findings raise concerns regarding procedures involving repeated metaphyseal perforations or aggressive curettage in pediatric patients. If vascular disruption plays a critical role in growth inhibition, careful surgical planning should be considered to minimize unintended long-term effects on bone growth.

Although this study provided novel insights into the effects of multiple metaphyseal holes on bone growth, it had certain limitations. While the sample size was typical for an animal study, it may have limited the statistical power and generalizability of the findings. Future studies with larger cohorts would help validate these results. First, the use of a rabbit model may have limited the direct clinical translation of these findings. Although rabbit tibiae share similarities with human long bones in terms of growth patterns, differences in bone remodeling rates and vascularization may influence the degree of growth modulation. Future studies using larger animal models (e.g., pigs or sheep) could help validate the clinical relevance of these findings. Second, the follow-up period was limited to 6 weeks, which may not fully capture the long-term effects of metaphyseal hole creation on bone growth. It remains unclear whether growth suppression in the two-hole group persists over time or whether compensatory remodeling occurs. Extended observation periods would provide a more comprehensive understanding of the durability of these effects and their persistence during skeletal maturity. Third, although histological and immunofluorescence analyses demonstrated reduced CD31 expression and fewer capillaries in the two-hole group, more detailed molecular investigations are required. Future research should assess additional angiogenic markers, such as

vascular endothelial growth factor and endomucin, to further clarify the mechanisms underlying growth suppression. Techniques such as quantitative polymerase chain reaction, western blotting, and micro-CT angiography can provide deeper insights into the effects of vascular disruption on bone growth.

In conclusion, a single metaphyseal hole filled with bone wax significantly stimulated long bone overgrowth, whereas creating an additional hole simultaneously resulted in notable growth suppression. Radiographic and histological analyses confirmed that the growth inhibition observed in the two-hole group was associated with reduced angiogenesis, as indicated by decreased CD31 expression. This study provides fundamental insights into the mechanisms underlying bone growth stimulation and inhibition, which may serve as a basis for future research and therapeutic strategies related to bone growth regulation. Further research is warranted to explore the therapeutic potential of targeted vascular interventions for growth modulation.

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AUTHOR CONTRIBUTIONS

Conceptualization: Kun Bo Park and Kyoung Mi Lee. Data curation: Kun Bo Park and Kyoung Mi Lee. Formal analysis: Kun Bo Park and Kyoung Mi Lee. Funding acquisition: Kun Bo Park. Investigation: Kyoung Mi Lee and Kun Bo Park. Methodology: Kyeong Hyeon Park, Byoung Kyu Park, and Hoon Park. Project administration: Kun Bo Park, Jin Woo Lee, and Hyun Woo Kim. Resources: Kyoung Mi Lee and Kun Bo Park. Software: Kyoung Mi Lee and Kun Bo Park. Supervision: Kun Bo Park, Jin Woo Lee, and Hyun Woo Kim. Validation: Won Myung Kim, Kyeong Hyeon Park, Byoung Kyu Park, and Hoon Park. Visualization: Won Myung Kim, Kyeong Hyeon Park, and Kyoung Mi Lee. Writing—original draft: Won Myung Kim, Kyeong Hyeon Park, and Kun Bo Park. Writing—review & editing: Won Myung Kim, Kyeong Hyeon Park, Kyoung Mi Lee, and Kun Bo Park. Approval of final manuscript: all authors.

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