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ORIGINAL ARTICLE

Bone Healing Properties and Biocompatibility of Locally-Made 1.5 System Titanium Implant in Rabbit Model

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ABSTRACT

Introduction: Treating maxillofacial fractures in Indonesia is costly, largely due to the reliance on imported miniplates and screws. This study evaluates the bone healing properties and biocompatibility of a locally manufactured 1.5 system titanium miniplate and screw implant, designed for internal fixation of maxillofacial fractures, as an alternative to imported options. **Methods:** Thirty *Oryctolagus cuniculus* species of rabbits were divided into two groups: locally made implants and control. A standardized osteotomy was performed on the right zygomatic arch of each rabbit, followed by internal fixation with 4-hole 1.5-system titanium miniplates and 5mm screws. Postoperative assessments included histopathological and radiographic evaluations on days 5, 28, and 56. ImageJ software was used to measure bone healing and inflammation for bone and muscle density, as well as peri-implant tissue responses. **Results:** Histopathological analysis revealed comparable bone healing in both the locally made and control groups, with inflammation peaking on day 5 and lamellar bone formation observed by week 8. The locally made implant group exhibited a higher percentage of lamellar bone formation (65.3% ± 3.7) compared to the control (52.2% ± 6.5, $p = 0.028$). Both groups showed no significant differences in metal debris, with no signs of foreign body reactions. Radiographic evaluation confirmed similar bone healing progress between groups, with inflammatory responses subsiding by day 28 based on muscle density measurements. **Conclusions:** The locally manufactured 1.5 system titanium miniplates and screws demonstrate bone healing properties and biocompatibility comparable to imported systems, offering a cost-effective alternative for maxillofacial fracture management in Indonesia.

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INTRODUCTION

The development of effective and biocompatible implants for midface fracture treatment is particularly important in regions facing economic constraints. Currently, our center relies on imported miniplates and screws, which come at a high cost due to import duties, logistics, and luxury goods taxes (1). At the Cleft and Craniofacial Center of Cipto Mangunkusumo Hospital, maxillofacial fractures are increasingly common, with Wibowo et al. (2018) reporting an average of 164 cases per year(1, 2). In the era of Universal Health Coverage in Indonesia, hospitals must manage high implant-related expenditures, which pose a significant financial burden. To mitigate these costs, locally manufactured implants provide a promising alternative by eliminating import-related expenses, including the minimum 10% luxury goods tax and associated logistical costs. (3). To address this, the locally produced 1.5-system miniplate and screw were developed in collaboration with the Research Center for Biomedical Engineering at Universitas Indonesia. These implants were made from medical-grade titanium alloy (Ti-6Al-4V), a material widely used in commercial implants for its proven biocompatibility (4, 5).

Despite using the same high-quality material as imported alternatives, the locally made implants must undergo rigorous testing to ensure they meet the necessary technical, biological, and metallurgical standards (6). In vivo testing in animal models is a crucial step in this process, providing valuable insights into bone integration and overall biocompatibility. These studies help identify potential adverse effects before progressing to clinical trials, ensuring the safety and efficacy of the implants for human use. In this study, rabbits were chosen as the animal model due to their anatomical similarities in midface structure to humans, making them ideal for evaluating bone healing and implant integration. Additionally, rabbits' accelerated metabolism enables the observation of long-term healing effects within a shorter timeframe, making them ideal for preclinical implant studies (7).

This study aims to assess the bone healing properties and biocompatibility of the locally-made 1.5 system titanium implant for midface fractures in a rabbit model. The data obtained from this animal study are critical for moving forward to clinical trials, as it is necessary to confirm the implant's safety and efficacy before its application in human maxillofacial fracture management.

Research Center for Biomedical Engineering in Universitas Indonesia had engineered the prototype of the locally made mini plates and screw with specifications similar to the universal 1.5 system of miniplate and screw. Preclinical studies, including ex-vitro biomechanical studies conducted in the Research Center for Biomedical Engineering Universitas Indonesia, resulted in comparable outcomes (8, 9). Rabbits show similarities in terms of the anatomical midface structure, thus had been frequently used in many prior studies on implants. Rabbits' metabolism is three times faster compared to the human. Therefore, the long-term effect of healing processes may be seen in a relatively short period (10-19).

MATERIALS AND METHODS

This study obtained ethical approval from ACUC no. 131-2018 IPB at Bogor Agriculture University. This study involved 30 male New Zealand White Rabbits (*Oryctolagus cuniculus*), each with a minimum weight of 3000 grams. Rabbits were divided into 2 groups using computerized randomization (Microsoft Excel); 1) the treatment group, in which osteotomy and fixation were performed using locally made implants, 2) the control group, in which imported Biomet® implants were used. The rabbits underwent right-sided zygomatic arch osteotomy and were fixed with titanium alloy implants according to their assigned groups. The dimensions of the plate were 17 x 4.0 x 0.6 mm, with screws measuring 1.5 mm in diameter and 4 mm in length for the imported implant. Additionally, the locally manufactured screws were 0.57 mm longer than the imported ones. Baseline radiographic images were taken immediately postoperatively. On days 5, 28, and 56, radiographic examinations were conducted, and the rabbits were sacrificed for histologic study. Out of 30 samples, 26 histology samples were successfully retrieved and analyzed. For the histological testing, each group had 4 samples on day 5, 5 samples on day 28, and 4 samples on day 56 (19) .

Surgical Procedure

During the procedure, the rabbits were sedated with 10-mg/kg ketamine and 3-mg/kg xylazine intramuscularly. The skin overlying the right zygoma was shaved and prepared for the aseptic procedure. Injection of supplemental local anesthesia, Lidocaine HCl and Epinephrine (Pehacain®) to the area of incision was administered to minimize bleeding and to approach with ease. The surgeon conducted a 2 cm incision on the right zygomatic arch, split the overlying muscle, and elevated the periosteum to expose the zygomatic bone. A chisel was used to create a line in the middle of the zygomatic arch, with no bone extracted. The fracture was fixed with implants according to the assigned group. In the first group, fractures were fixed with two Biomet® titanium 1.5 mm miniplates and 8 screws. In the second group, fractures were fixed with two locally made titanium 1.5 mm miniplates and screws. The wound was then closed with 4/0 Prolene sutures. (11, 13, 15). All animals were kept and fed under similar conditions postoperatively and evaluated by the attending veterinarian. Each animal received antibiotic Amoxicillin (10mg/kg intramuscularly) and analgesic Flunixin Meglumine (1.1 mg/kg intramuscularly), both twice a day for three days.

Histological Study

The implanted zygomatic arch with the surrounding muscle was retrieved and fixed in 10% formalin for at least 48 hours. After the bone specimens were decalcified in 20% nitric acid for one week, the implants and screws were removed. The specimens were then processed through several steps, including trimming, dehydration, embedding, and cutting, to prepare them for histological slides. Finally, the samples were stained with hematoxylin-eosin. The slides were then examined under a light microscope to compare changes related to the bone healing rate, inflammation, and foreign body reaction in the bone and surrounding tissue. The area chosen for histological evaluation was the region along the fracture site, examined at 10x magnification. The samples were examined randomly, and assessors were blinded to the group assignments of the slides to ensure unbiased analysis. The peri-bone-implant area was evaluated for the inflammatory cells, and the appearance of giant body formations was counted and expressed on the table as a number/quantity (numeric variable). ImageJ 1.50i software was used to calculate the percentage area of various parameters at the fracture site, including granulation tissue, fibrocartilage, new bone formation, and woven and lamellar bone formation. Measurements were performed by selecting areas and stain intensity specific to each parameter, allowing for precise quantification of the extent of tissue changes at the fracture site.(17) Metal debris was assessed as apparent and not apparent. Quantitative parameters were analyzed using the Independent T-Test, while the Fisher Exact Test measured qualitative parameters.

Radiological Test

Two ventrodorsal and latero-lateral radiological views were obtained using a conventional X-ray machine. (Figure 1) The image was then translated into a digital image using The IM3 CR 7 Vet Advanced Digital X-Ray.

PhotoScape X software was used to standardize the image size by pixels (between 625-635 x 390-395 pixels), showing only the zygomatic arch area. To measure the density of the bone that represents bone healing and muscle that represents the surrounding tissue reaction to the implants, the authors used ImageJ 1.50i software. The density elicited results in an *arbitrary unit*, which signifies the density of the bone and muscle compared to radiological background, which is regarded as the density of air (17).

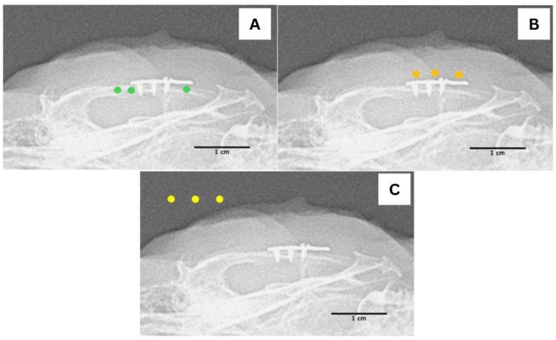

Figure 1. a) The three points were taken at the zygomatic arch for bone density, b) Muscle density is the mean of 3 points taken on the soft tissue just above the implant, c) The density of backgrounds (air) as the standard for the possibility of different opacities of the x-rays.

RESULT

Thirty samples were retrieved for histological preparation; however, four were damaged during tissue preparation. In total, 26 of 30 histology samples were successfully retrieved to be analyzed (control n= 13 and treatment n=13). We did not observe any infection, seroma, and hematoma during observation of 5 days, 28 days, and 56 days. Data on histological examination can be seen in Table I.

Histological examination of the inflammatory cells and the granulation tissue began to fill the fracture gap on day 5. The proportion of granulation tissues and fibrocartilage calluses dominated the fracture site in both groups. Despite the formation of woven and lamellar bone initiated in several fracture and screw sites, the inflammatory cell count was highest on day-5 observation and showed no significant difference between the two groups. (Figure 2) Metal debris was seen around the screw area in both groups.

On day-28, the inflammatory cells and the granulation tissue had reduced quantity. The fracture site has been filled with new bone formation (woven and lamellar bone), despite the occasional presence of fibrocartilage and granulation tissues in between. The proportion of new bone formation was similar in both groups with an insignificant difference, with higher proportion of lamellar bone compared to woven bone (treatment lamellar: woven bone = 41.6 (±8.6): 28.6 (±11.7); control lamellar: woven bone = 35.6 (±15.6): 28.2 (±8.25)). We observed that metal debris is apparent around the screw site in all the samples of both groups. The metal debris seemed to hardly provoke any giant body formation and inflammatory cells, proven by the low quantity of inflammatory cells and giant body formation around the screw site. This resulted in a statistically insignificant difference between groups (Table I).

On day-56, the granulation and fibrocartilage tissues at the fracture sites were minimal, with similar findings in both groups. The fibrocartilage tissue of the treatment group was lower than control (treatment 6.7(±6.4) and control 17(±3.3) with p=0.038). The new bone formation had filled the entire fracture site in both groups (Figure 3). The new bone formation in the fracture site was dominated by lamellar bone, which was higher in the treatment group (treatment 65.3 (±3.7) compared to control group 52.2 (±6.5) with p= 0.028). The inflammatory cells and giant body formation remain similar to the previous count. Meanwhile, metal debris was found in 4 out of 4 samples of the treatment group and 3 out of 4 samples in the control group with insignificant difference between both groups (p=1.000).

Table I. Histopathological Data

Days	Histopathological Data	Treatment (n: 13)	Control (n: 13)	P value
5 Days	Inflammatory Cells (n)	60.5 (±16.1)	59.5 (±26.4)	0.951
	Giant Body Formation (n)	2.25 (±0.95)	0.75 (±1.5)	0.143
	Granulation (%)	41 (±11.5)	39.5 (±10.9)	0.857
	Fibrocartilage (%)	31 (±12)	40.2 (±11.5)	0.299
	Woven Bone (%)	27 (±4.9)	19 (±10.42)	0.215
	Lamellar Bone (%)	0	0	0
	Metal Debris (n/total)	3(4)	4(4)	1.000
28 Days	Inflammatory Cells (n)	28.4 (±8.6)	24 (±14.7)	0.581
	Giant Body Formation (n)	2.2 (±2.16)	1.4 (±1.34)	0.503
	Granulation (%)	16.2 (±9.5)	13.6 (±5.3)	0.611
	Fibrocartilage (%)	10.2 (±7.2)	20.6 (±13.1)	0.158
	Woven Bone (%)	28.6 (±11.7)	28.2 (±8.25)	0.952
	Lamellar Bone (%)	41.6 (±8.6)	35.6 (±15.6)	0.487
	Metal Debris (n/total)	5(5)	5(5)	-
56 Days	Inflammatory Cells (n)	22 (±4.3)	20.75 (±1.9)	0.623
	Giant Body Formation (n)	0.33 (±0.57)	1.25 (±1.5)	0.370
	Granulation (%)	9 (±6.9)	6.5 (±3.1)	0.542
	Fibrocartilage (%)	6.7 (±6.4)	17 (±3.3)	0.038*
	Woven Bone (%)	17.67 (±9.8)	24.5 (±7.4)	0.340
	Lamellar Bone (%)	65.3 (±3.7)	52.2 (±6.5)	0.028*
	Metal Debris (n/total)	4(4)	3(4)	1.000

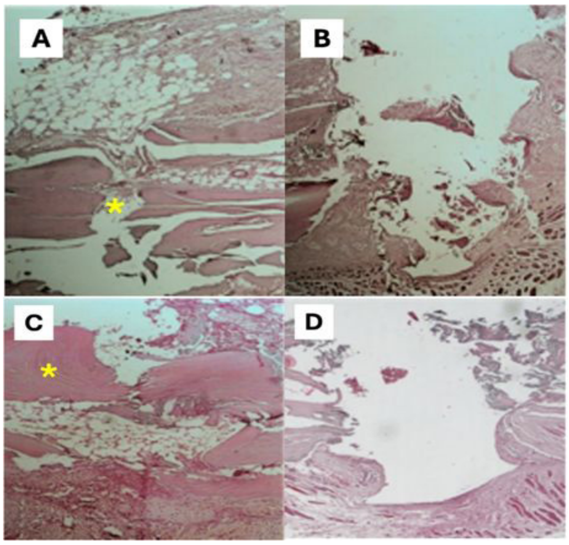

Figure 2. Histological findings on day five after the osteotomy and plating: (A and B) treatment group; (C and D) controlled group. The residual hematoma and various inflammatory cells were seen around the fracture site. The fracture sites were partially infiltrated by the new bone formation

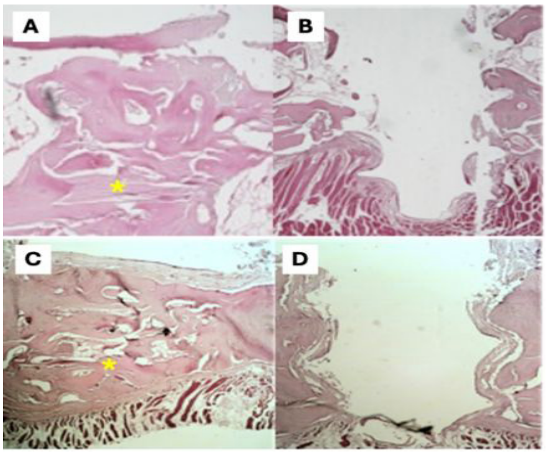

Figure 3. Histological findings on day 56 after the osteotomy and plating: (A and B) treatment group; (C and D) control group. The lamellar bone is dominating the fracture site.

In radiologic evaluation, the bone density of the zygomatic arch increased following internal fixation (Table II). However, this was not apparent on day-28, of which the decrease of bone density is more prominent in the control group (mean 42.6 to 34.5). Generally, the bone density was higher in the locally-made group compared to the control group. Nevertheless, this was regarded as statistically insignificant.

Table II. Mean value of bone and muscle density, analysis test using T-test

Time	Control			Locally made			*p*
	N	Mean	SD	N	Mean	SD	
Bone Density							
Immediate PO	15	34.7	7.5	15	37.2	9.1	0.805
POD 5	15	42.6	5.2	15	44	6.4	0.689
POD 28	10	34.5	4.2	10	43.4	5.7	3.924
POD 56	4	42.7	8.1	4	46.5	2.8	0.865
Muscle Density							
Immediate PO	15	24.4	7.8	15	27	7	0.959
POD 5	15	31.7	6.6	15	32.2	8.1	0.816
POD 28	10	23.7	4.7	10	29.6	7	2.195
POD 56	4	29.2	6	4	33.2	7.7	0.619

Muscle density may be used to indicate the surrounding tissue's reaction to implantation following osteotomy in the form of an inflammatory response. The highest tissue density was observed on day five as the inflammation peaked and subsequently diminished. There were differences in the value of bone density between the two groups, despite being statistically insignificant. On day-56, both groups showed another rise in muscle density (Table II).

DISCUSSION

Biocompatibility and mechanical endurance are the most crucial properties of both temporary and permanent implants. The material must also be biologically stable due to its interaction with soft and hard tissues, blood, and intra and extracellular fluids of the human body (19).

Before a novel medical device can be safely applied in clinical settings, it must undergo rigorous evaluation to mitigate potential risks. This process typically involves multiple stages, including material testing, in vitro screening, and in vivo testing of the final product. Among these stages, animal experimentation plays a critical role in advancing new medical technologies, particularly in assessing the safety, efficacy, and biocompatibility of innovative devices. Animal studies provide essential insights into the bone healing capabilities and performance of newly designed miniplates, offering valuable preclinical data that cannot be fully replicated through in vitro methods alone (6).

Selecting a suitable animal model is crucial for studying bone healing and biocompatibility. In this study, rabbits were chosen to evaluate the performance of locally-made 1.5-system titanium implants. Rabbits are widely used in research involving mini plates and screws due to their accessibility and manageable size. Laurenzo et al. noted that midface maturity in rabbits is achieved by week 20, which served as the inclusion criterion for this study (19). However, using rabbit models for midface fracture studies presents certain limitations. Notably, bone density and fracture dynamics in rabbits differ significantly from those in humans, which may affect the generalizability of the findings. During surgery, the zygomatic bone of rabbits was found to be fragile, making it challenging to create a single osteotomy line. As a result, some rabbits exhibited comminuted fracture lines, complicating the study of fracture healing.

While the tibial bone is often considered a more suitable site for implantation due to its rigidity—potentially mimicking human midface buttresses—the forces applied to this bone may not accurately replicate those experienced in human facial fractures (11, 15, 18, 19). Microscopically, rabbit bones have thinner cortices and less cancellous bone compared to human bones. Additionally, the facial bones of rabbits are notably thin, which further limits their comparability to human facial structures. Despite these differences, the bone healing properties of rabbits are similar to those of humans in terms of bone metabolism, which follows a Haversian-type remodelling process, albeit at a higher rate than in humans. This similarity makes rabbits a valuable model for studying certain aspects of bone healing, even though their structural and mechanical properties differ (7).

The observation was done on days 5, 28, and 56 post-operation to better understand bone healing properties and biocompatibility. Postoperative day 1 was measured as a baseline; day 5 represented the acute phase of bone healing, while day 28 showed the mid-process of bone healing, and day 56 showed complete bone healing. The healing process is affected by the extent of damage to soft and hard tissue and the vascular supply caused by both the fracture and the fracture treatment. There are some variations in the repair of different types of bones with rigid internal fixation in many kinds of literature (20-25).

This study observed excellent soft tissue healing without complication in all samples. From the histological study, both groups showed inflammatory cells peaked on day five and decreased on days 28 and 56 with no significant difference. These results reflect that the inflammatory response follows the bone healing phase, which shows that the biocompatibility of the locally-made implant is comparable to the control group.

The presence of fibrocartilage tissue showed a significant difference on day 56 of observation, with the control group still exhibiting a slightly greater amount of fibrocartilage tissue compared to the treatment group. This difference may be attributed to variations in the bone healing process between the two groups. In this study, direct bone formation through contact healing did not occur, as also noted by Sverzut et al. (2008) and Freitag et al. (1996) (26, 27). Contact healing requires direct contact between bone fragments, but the osteotomy procedure in this study rarely resulted in a simple, non-gapped fracture line, and there was considerable variation among samples. As a result, secondary bone healing, which involves an intermediate fibrocartilage phase before bone remodelling, became the predominant healing mechanism. This could explain why fibrocartilage remained more evident at this stage, particularly in the control group, where healing may have progressed more slowly. Although some literature considers direct healing to be the ideal outcome in fracture repair, secondary bone healing has not been shown to be significantly less effective in many cases.

Consistent with this healing pattern, woven bone formation was observed as early as day 5 and progressively increased over time. By day 56, new bone formation had peaked in both groups, with most of the woven bone transitioning into mature lamellar bone. However, the treatment group exhibited a significantly greater amount of lamellar bone than the control group, suggesting that the locally made titanium implant may have facilitated a more efficient remodeling process. Bone remodeling typically occurs over a period of 3 to 6 months and can continue for years, during which woven bone is gradually replaced by lamellar bone through osteoblastic and osteoclastic activity, driven by mechanical stress (28). These histological trends are consistent with findings from studies conducted by Hirai et al, as well as Millar et al which reported similar remodeling patterns and bone healing progression (29, 30).

Histological examination also revealed that granulation tissue and fibrocartilage were most prominent on day 5 before decreasing over time, aligning with the expected progression of the inflammatory phase in bone healing (31). By day 56, the bone samples had healed satisfactorily, marking a transition into the remodeling phase, which typically lasts between 3 to 6 months and can continue for years. During this phase, woven bone is completely replaced by lamellar bone through coordinated osteoblastic and osteoclastic activity in response to mechanical stress (12).

Metal debris, characterized by irregular black fragments measuring between 1 and 3 μm, was observed in the surrounding soft tissue following implant insertion. Similar findings have been reported in previous studies, with many of these fragments being phagocytosed by macrophages (32, 33). However, in this study, the presence of metal debris did not appear to provoke a significant foreign body reaction, further supporting the biocompatibility of the locally made implant.

Radiological analysis provided further insights into bone healing progression and soft tissue reactions. Postoperative day 1 was measured as the baseline, with day 5 representing the acute inflammatory phase of bone healing. By week 4, healing was well underway, and by week 8, bone healing was considered complete. The results showed that bone density reached its highest point at week 8 in both groups, consistent with the findings of Atali et al (12). However, although not statistically significant, the higher density observed in the locally made implant group was likely influenced by the thickness of the miniplate, which may have created a halo sign. This optical artifact occurs when there is a contrast between two structures with very different densities. To minimize this potential bias, future studies should closely examine each radiographic image for evidence of the halo effect. If detected, digital image processing techniques should be applied, such as decomposing images into frequency bands, eliminating low-frequency components, and then reassembling them for more accurate interpretation (34).

Muscle density was used to evaluate the soft tissue reaction around the implantation site. Surgical trauma to the muscle overlying the bone naturally triggered an inflammatory response, which was reflected in the highest muscle density readings on day 5 in both groups. This reaction subsided by week 4 but increased again by week 8. A similar trend was reported in the study by Atali et al. (2016), which examined rabbit mandibles and found evidence of woven bone formation at various stages of maturity within calluses over 12 weeks. Despite the significantly higher bone density observed at week 12 compared to week 4, the study suggested that complete bone healing may not yet be achieved by the third month. This could explain why muscle density around the implant site increased again after initially decreasing at week 4 (12).

The thickness and surface characteristics of the miniplate may have also influenced the results. Although statistical analysis did not show a significant difference, the locally made implant group exhibited slightly higher muscle density, possibly due to the miniplate's thickness and surface smoothness. These findings provide valuable input for implant design improvements. Future engineering refinements should focus on optimizing miniplate thickness, pliability, and surface smoothness to enhance clinical performance and minimize potential biases in radiological assessments.

Overall, these findings highlight the promising bone healing properties and biocompatibility of the locally made 1.5 system titanium implant. While histological and radiological results suggest that the implant supports secondary bone healing and efficient remodelling, further studies with longer observation periods and standardized osteotomy techniques are recommended to confirm its long-term clinical applicability.

CONCLUSION

The locally made titanium implants possess material properties and dimensions comparable to commercially available implants. This animal study demonstrated that the locally made miniplates and screws exhibit excellent biocompatibility and bone healing properties, with no significant complications observed in soft tissue healing. Additionally, histological and radiological findings showing similar trends between the treatment and control groups

Based on these findings, we conclude that the locally made 1.5-system titanium implant meets preclinical safety and efficacy standards for bone healing. The study successfully establishes Stage 0 (preclinical phase) of implant development, confirming that these implants provide comparable performance to commercially available alternatives. While further clinical trials are required, the results strongly support the use of these implants in subsequent human studies. Future research should focus on refining miniplate design, particularly in terms of thickness, pliability, and surface smoothness, to optimize clinical outcomes.

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Not applicable

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