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A Novel Nano-Synthetic Hydrophilic Bone Graft (OsteoFlo HydroFiber) Is a Non-inferior Alternative to Iliac Crest Autograft in a Rabbit Posterolateral Fusion Model

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Abstract

Study Design: Experimental.

Objectives: The objective of the study was to evaluate the in vivo performance of SurGenTec OsteoFlo HydroFiber™ (OF-HF) (test material), compared to autograft (ICBG) in an established posterolateral spine fusion rabbit model. The test material was evaluated as a stand-alone and extender product with autograft (1:1).

Methods: Sixty-nine skeletally mature male New Zealand white rabbits underwent a single-level bilateral posterolateral intertransverse process spinal fusion at the L5-L6 level. Animals were randomly assigned to one of three groups: ICBG, ICBG + OF-HF, or OF-HF. Outcomes were assessed at 4 (N = 5/group), 8 (N = 8/group), and 12 weeks (N = 10/group) evaluating for spine fusion rate, new bone formation, graft resorption, and inflammatory response using radiographic, microCT, biomechanical, and histological endpoints.

Results: In general, all animals appeared to be in good health both at the start and conclusion of the study. All previously mentioned fusion assessment methods at 12 weeks demonstrated a 60% fusion rate for the ICBG and OF-HF groups, while the ICBG + OF-HF group demonstrated a 50% fusion rate. MicroCT morphometric analysis showed the OF-HF groups to have a significantly greater bone volume ($P < 0.05$) at 12 weeks compared to the ICBG group.

Conclusions: The comparable fusion rates, combined with the significantly increased bone volume in both groups containing OF-HF at the 12-week interval demonstrates the OF-HF graft to be a non-inferior alternative to ICBG for stand-alone use or as an autograft extender.

Background

Posterolateral spinal fusion (PLF) is a widely used technique to address conditions in the lumbar spine, including degenerative disc disease and spondylolisthesis. PLF involves fusing adjacent vertebrae using bone grafts with iliac crest bone graft (ICBG) considered the gold standard in experimental rabbit models due to its osteogenic, osteoinductive, and osteoconductive properties, and a lack of host bone in rabbits.[1-9] ICBG can be harvested from the donor and the harvesting is associated with an increased risk of complications, including increased morbidity, secondary site infections, chronic pain, pseudoarthrosis, gait disturbances, and has a

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limited volume that can be obtained.[1-3,5,10-14] In fusions using ICBG, reports have shown as many as 60% of patients have chronic pain two-years postoperatively from their harvest site.[15] These limitations have led to development of alternative graft substitutes, extenders, and void fillers to decrease reliance on ICBG for arthrodesis. These substitutes can generally be classified as allografts, demineralized bone matrices, autologous growth factors, collagen matrices with bone morphogenic proteins (BMPs), and ceramics.[6,7] Silicate carbonate apatite, when infused with collagen, have been shown to be effective in delivery of osteogenic factors to promote bone formation, but these formulations often lack the consistent osteoinductive and osteogenic capabilities of ICBG.[16-19]

An innovative alternative, OsteoFlo HydroFiber™ (OF-HF), a nano-synthetic hydrophilic bone graft, was developed (SurGenTec, Boca Raton, Florida) and is a novel formation of silicate carbonate apatite, and carriers combined with infused collagen. The use of silicate carbonate apatite mixed with collagen has been demonstrated to promote superior mechanical strength compared to grafts using calcium phosphate-based ceramics,[20,21] and possess osteoinductive properties to accelerate bone healing.[22] OF-HF is composed of hydrophilic web-like fibers interwoven with porous synthetic particles forming a cohesive structure. The cohesive properties allow the graft to be highly flowable while preventing migration and providing easier handling during surgery. Unlike other graft types, the porosity of silicate carbonate apatite allows collagen formation on the glass surface, promoting bonds to connective tissue, inhibiting migration.[19] The OF-HF graft is customizable, allowing reconstitution with saline, blood, or bone marrow aspirate (BMA) allowing the desired consistency to be obtained for use in a variety of settings.[19] Recombination with BMA can turn OF-HF into a live graft with cellular content.

Calcium sulfate bone grafts have been shown to be an osteoconductive substitute to ICBG, but are limited by the quick resorption rate of 1-3 months,[22] which is faster than the rate of new bone deposition.[23] OF-HF has demonstrated to provide controlled expansion to supply continuous stable scaffolding between bone interfaces for optimal area for fusion to take place and the microstructure facilitates the delivery of osteoinductive factors. Additionally, the OF-HF graft is an FDA cleared equivalent to autograft for stand-alone use in interbody cages, disc space, and posterolateral fusions, or may be mixed seamlessly with ICBG as a bone graft extender.

The purpose of this study was to investigate and compare the spinal fusion performance of OF-HF and OF-HF with ICBG compared to ICBG alone using an established posterolateral spinal fusion rabbit model. Fusion rates, new bone formation, graft resorption, and inflammatory response were assessed to evaluate performance.

Methods

The rabbit posterolateral fusion model is a well-established tool used for evaluation of graft performance.[24,25] In the definitive outcomes timepoint, a power analysis determined a sample size of 10 motion segments per treatment group, ensuring a 20% difference in flexibility testing could be observed (alpha = 0.05, power = 0.90%). All procedures were performed in a standard operating suite at an animal research surgicenter by a single surgeon with over 20 years of experience. All procedures were approved by the Institutional Animal Care Use Committee (#0041977 and #3011977). Throughout the study, animals were individually housed and monitored at least twice daily to assess for signs of pain and/or discomfort.

Graft Preparation

OF-HF Graft

The OF-HF graft is a novel formation composed of a blend of carbonate apatite and silicate particles within a proprietary carrier and type-1 collagen. For investigational implant preparation, the graft was aseptically removed and hydrated with 2.0 mL of saline per 3.0 mL of graft material. The hydrated fibers were then thoroughly mixed with particles until fully embedded in collagen. Once the mixture was cohesive, the desired consistency was achieved. The mixture was then carefully pulled apart and recombined multiple times to ensure graft was homogenous.

Autologous Bone Graft

The caudal aspect of the midline incision was utilized to access the iliac crests bilaterally. Approximately 3 cc of cortico-cancellous bone was harvested from both iliac crests using a Miltex Rongeur.

In the OF-HF + ICBG group, 1.5 cc of cortico-cancellous bone was harvested from each iliac crest using a Miltex Rongeur. The harvested bone was then manually combined with the OF-HF graft to create a homogenous mixture.

Animal Model and Surgical Procedure

Sixty-nine skeletally mature male New Zealand white rabbits underwent a single-level bilateral posterolateral intertransverse process spinal fusion at the L5-L6 level in a surgical suite using aseptic techniques. Skeletal maturity was confirmed prior to study enrollment through radiographic confirmation of proximal tibia and distal femur growth plate closure.

Animal sedation was induced using a mixture of ketamine HCL (26.0 mg/kg), xylazine (0.78 mg/kg), and acepromazine (0.15 mg/kg), plus butorphanol (0.5 mg/kg) via intramuscular injection. Anesthesia was then maintained through isoflurane inhalation (1.5-3%) with 100% oxygen. Once anesthetized, blood was harvested from the auricular artery prior to surgery to assess animal health. To prevent infection, prophylactic

Table 1. Number of Animals per Treatment Group. Rabbits Were Randomly Assigned to Treatment Groups and Timepoints Prior to Surgery. All Groups Received Approximately 3.0 cc of Their Assigned Graft

	Graft volume per side		Time point (euthanasia)			
Test group	Autograft	OF-HF	4 wk	8 wk	12 Wk	Subjects (n)
ICBG	3.0 cc	—	5	8	10	23
ICBG + OF-HF	1.5 cc	1.5 cc	5	8	10	23
OF-HF	—	3.0 cc	5	8	10	23

cefazolin (13 mg/kg) was administered parenterally preoperatively and then twice daily for 48 hours postoperatively.

Rabbits were placed prone on the operating table and prepped with 70% povidone/iodine (Betadine) solution. The surgical approach to the spine was identical in all rabbits. A dorsal midline skin incision was made from L1 to the sacrum. Bupivacaine (0.5%) or Lidocaine (2%) was applied to the fascia over surgical sites prior to incision and then the fascia and muscle were incised over the L5-L6 transverse processes (TPs). The TPs were then carefully decorticated using a high-speed burr until bleeding host bone was visualized. The vertebral bodies and laminae remained untouched throughout the procedure.

The animals were randomly assigned into three groups by simple randomization whereas timepoints were not known to the surgeon: (1) ICBG, (2) ICBG + OF-HF, and (3) OF-HF (Table 1). For each group, approximately 3.0 mL of graft material was placed in the paraspinal bed between the TPs on each side, as this is the maximum amount of bone graft that can be harvested from the iliac crests without significant animal morbidity.[24,26,27] The graft was placed in the medial 1/3 to 1/2 of the TPs with extension towards the lamina. Following graft placement, the muscle layers were allowed to return to their native positions, and the fascia and skin were closed with 3-0 absorbable sutures, with the skin stapled. Staples were removed after 14 days.

Post-operatively, analgesics were administered to ensure animal comfort. The animals were housed individually and fed *ad libitum*, with twice daily observation. Additional pain medication was given based on mobility, diet, disposition, and general activity signs that would signal increased pain. Animals were radiographed at 4-week intervals until euthanasia. Animals were humanely euthanized at 4 weeks (n = 5/group), 8 weeks (n = 8/group), and 12 weeks (n = 10/group).

Radiographic Analysis

Ventral/Dorsal radiographs were obtained using a Simon DR (Quantum) RAD-X High Frequency Radiographic Imaging System (model: E7242X) and stored with a Carestream PACs system. Radiograph films were evaluated for signs of graft migration, osteolysis, fracture, and/or any other adverse events. Additionally, radiographs were assessed for bilateral fusion by three reviewers blinded to treatment group and time point. Term radiographs were assessed for fusion by comparing trabecular bone patterns, change in implant appearance, and graft density to immediate post-op radiographs. Final fusion confirmation was determined by agreement of at least two out of three reviewers.

Five specimens of each implant type and timepoint were scanned using a SkyScan 1276 Micro-CT scanner. Internal structures were reconstructed as a series of 2D cross-sections which to analyze morphological and morphometrical parameters of the specimen. The SkyScan 1276 was calibrated per the manufacturer's recommended schedule for contrast, positioning, and density. A region of interest (ROI) encompassing the entire fusion mass (inclusive of the TPs sagittal plane, bilateral, center of defect) was used to calculate bone and implant volumes.

Manual Palpation

Flexibility testing of the fused motion segment was assessed by manual palpation according to established protocols.[24,28-30] After spine removal, fusion was graded by three independent, blinded observers. A segment was classified as "fused" if no detectable motion was observed at the disc space during flexion, extension, and lateral bending. The segment was designated as "not fused" if motion was detected at the disc space. Bilateral fusion status was assessed by evaluating lateral bending and cranial/caudal compression of the adjacent TPs on both sides. Final fusion status was determined by 100% agreement of the observers.

Histology

Five specimens from each treatment group and time period (same specimens as uCT) were selected for histological evaluation. Fusion sites of each animal were processed for histology and sectioned in the sagittal plane to obtain a total of six sections per animal (3 per side of the fusion mass). Sections were created from each side, through the center of the fusion mass, and through the medial and lateral aspects of the fusion mass, spaced approximately 3 mm apart. Sections were subsequently stained with hematoxylin & eosin (H&E).

Semiquantitative histopathology analysis was performed on all six sections from each fusion mass (3 per side) by the PI and a

Table 2. Radiographic Fusion Results. Fusion was Assessed by Three Blinded Reviewers With Agreement of at Least two of the Three Observers Required to Determine fusion Results

	4 Weeks	8 Weeks	12 Weeks
Test group	% fused	% fused	% fused
ICBG	40% (2/5)	50% (4/8)	60% (6/10)
ICBG + OF-HF	0% (0/5)	50% (4/8)	50% (5/10)
OF-HF	0% (0/5)	38% (3/8)	60% (6/10)

board-certified veterinary pathologist. The sections were assigned scoring based on ISO 10993-6, Annex E. An overall assessment was recorded for each fusion mass (one score per side).

Statistical Analysis

Statistical analysis was performed on the microCT analysis. All data was analyzed to a 95% confidence level using a two-tailed t-test assuming unequal variance in Microsoft Excel. Unless otherwise specified, results are presented as the mean ± one standard deviation.

Results

The surgery procedures were uneventful, with all grafts successfully administered. All animals were alert and eating within three hours postoperatively. All rabbits were determined to be in general overall health through twice-daily observations of each animal and hematological analysis at time of surgery and euthanasia with no animals omitted from the study. Those in the ICBG treatment group exhibited decreased fecal/urine output and decreased food consumption during the first week following surgery; however, these parameters returned to normal within 14 days. At the time of euthanasia, all rabbits were in good health, regardless of treatment group. No remarkable abnormalities were noted of the external surfaces, orifices, cranial, thoracic, abdominal, and pelvic cavities through necropsy. Macroscopic analysis of the implant sites showed no apparent adverse effects surrounding the fusion sites.

Radiographic Analysis

A normal healing response with no adverse reactions was observed at 4, 8, and 12 weeks across all test groups. Proper graft implantation through post-op radiographs that was maintained throughout the study. Minor graft migration was observed from immediate post-op radiographs to later radiographs and is a common occurrence with synthetic spinal grafts due to compression forces from overlying musculature.[6]

Fusion rates were assessed through radiographic criteria (Table 2). There was 100% agreeance amongst observers at all three timepoints. At 4 weeks, the ICBG group demonstrated a 40% fusion rate, while no fusion was observed in the other test groups at this time. A similar incidence of bilateral fusion was observed at 12-weeks for all three test groups, with ICBG and OF-HF groups demonstrating a 60% fusion rate and the ICBG + OF-HF group demonstrating a 50% fusion rate ($P = 0.67$).

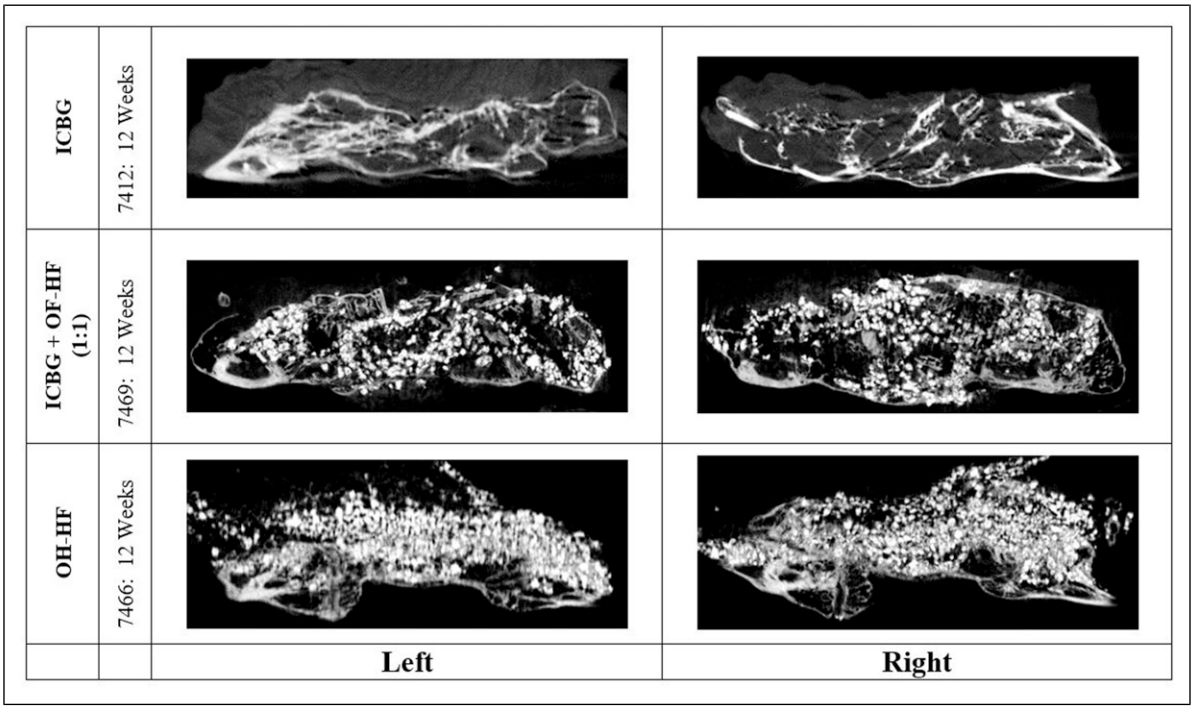

Figure 1. Micro-CT sagittal sections of each test group at 12 weeks

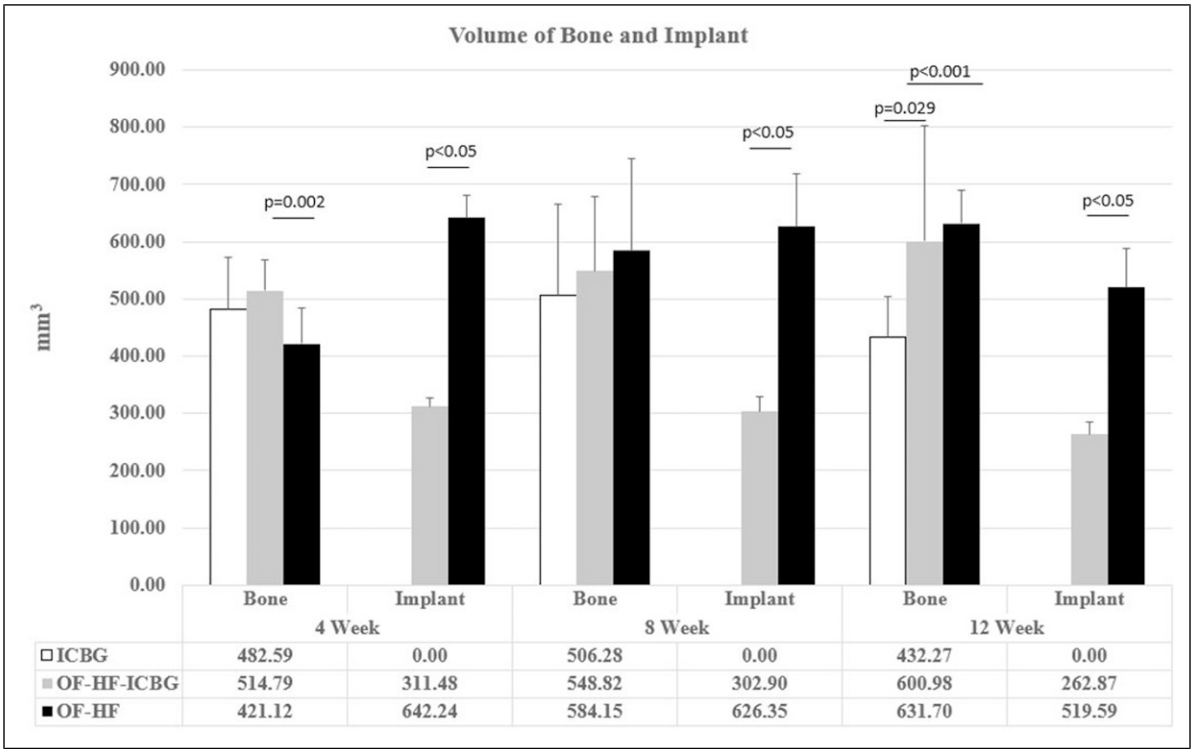

Figure 2. MicroCT Mean Volumes of Bone and Implant. MicroCT analysis was performed using a SkyScan 1176 microCT scanner and reconstructed using the parameters: smoothing – 2, ring artifact – 5, beam hardening – 54, and compressed sensing – 0.0-0.05. A ROI that encompassing the entire fusion mass (inclusive of the transverse processes sagittal plane, bilateral, center of defect) was used to calculate bone and implant volumes. The results given show the mean + one standard deviation

A normal healing response occurred with no adverse reactions observed across all three test groups. MicroCT scans at 4 weeks revealed host integration and new bone formation from the TP margins across all animals, (Figure 1). These findings supported the radiographic assessments, with complete bridging cortical shell observed in all animals determined to be fused through radiographic analysis.

MicroCT morphometric analysis using an ROI encompassing the entire fusion site, including the TPs, was performed to quantify the volumes of bone and implant at each time point (Figure 2). Eight- and twelve-week scans demonstrated a continuation of new bone formation and graft remodeling from the four-week time point. At 12 weeks, a significantly greater bone volume was observed in the OF-HF group (631.70 mm^3) compared to the ICBG group (432.27 mm^3) ($P < .001$), while no statistical differences in bone volume were observed at earlier timepoints.

Manual Palpation

Manual palpation of the treated spinal segments was used to assess lateral bending, revealing the same distribution of fusion status across all groups at all timepoints as observed in radiographic analysis (Figure 3). At 4 weeks, all three observers agreed there was a 40% fusion rate in the ICBG group, while no fusion was detected in other groups. Similarly, all observers determined the ICBG and OF-HF groups both demonstrated a 60% fusion rate at 12 weeks, whereas the ICBG + OF-HF group demonstrated a 50% fusion rate ($P = 0.67$).

Histopathology

Implanted material, (eg, ICBG or OF-HF) at time points (Week 4, 8, or 12), in the treatment sites were generally characterized by the presence of abundant implanted material, the amount of which typically decreased over time (ie, on average moderate to moderate/marked), Figure 4.

The area within the treatment sites and surrounding the implanted material was generally infiltrated widely by variable amounts of supportive mesenchymal tissue, bone marrow elements and/or new bone, with variable amounts of fibrous connective tissue which was overall (ie, on average) minimal to mild in magnitude and generally observed at the periphery of the sites. Neovascularization within the treatment sites was generally minimal, regardless of implanted material or timepoint.

Evidence of the re-establishment of bone marrow elements (eg, marrow adipocytes and/or hematopoietic cells) was observed at Week 4, most notably in the ICBG group (mild/

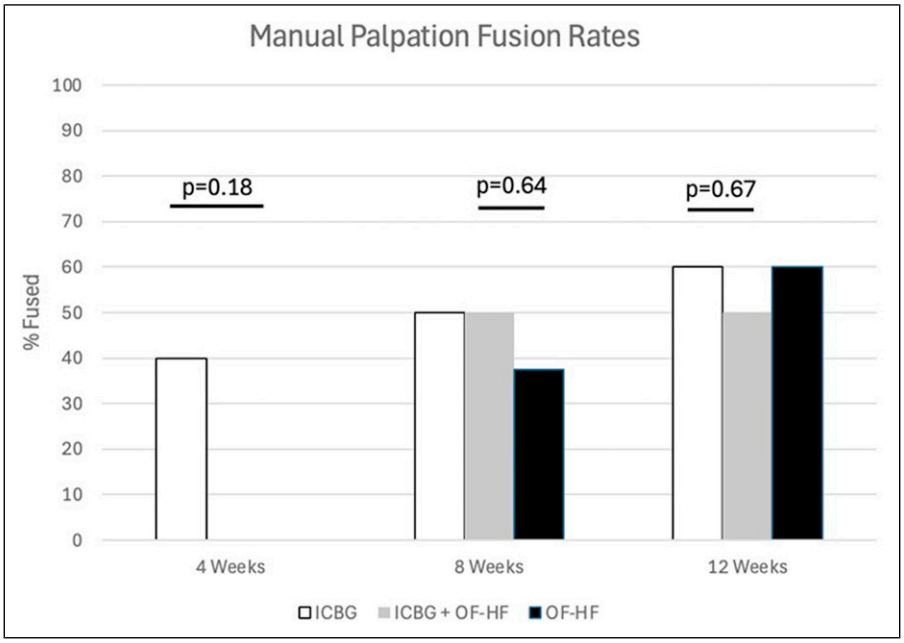

Figure 3. Manual Palpation Fusion Rates. Fusion was assessed by three blinded reviewers with agreement of at least two of the three observers required to determine fusion results. All *P*-values were above 0.05, demonstrating no significant difference among fusion rates

moderate) compared to the OF-HF groups (absent). At Week 8, both the ICBG and OF-HF groups exhibited moderate bone marrow tissue within the sites and all groups were interpreted to exhibit comparable bone marrow re-establishment by Week 12 (ie, on average, all groups moderate).

Regardless of implanted material or timepoint, evidence of material-related cellular infiltrates (eg, 'inflammation') was minimal and typically characterized by scattered histiocytes/macrophages and/or multinucleated giant cells. There was no evidence of adverse inflammation (eg, exuberant neutrophilic or granulomatous) or infection.

There was no evidence of necrosis, degeneration, non-marrow adipose 'fatty' infiltration, or exuberant responses (eg, fibrosis).

Discussion

Due to the increased morbidity associated with ICBG use, there has been a growing demand for the development of synthetic bone grafts capable of achieving reliable bony fusion.[31] This study served to evaluate the performance of the OF-HF graft, both for stand-alone use and as an autograft extender, in a well-established PLF rabbit model. The outcomes were assessed through manual palpation, radiographs, microCT, and histology at 4-, 8-, and 12-weeks examining spine fusion rate, new bone formation, graft resorption, and inflammatory response. Based on the observed findings, the OF-HF bone graft demonstrated biocompatibility and performed comparably to ICBG in the PLF procedure.

This study confirms the efficacy of the OF-HF graft for both stand-alone use and as an autograft extender. A normal healing response was observed across all test groups, and the 60% fusion rate demonstrated by the ICBG group is consistent with previous studies at this institution[6,7,32,33] and others.[24,34-36] Comparable fusion results were obtained for all groups by all assessment methods, with a 60% fusion rate for the ICBG and OF-HF groups, and a 50% fusion rate for the ICBG + OF-HF group, with no statistically significant differences in fusion status at 12 weeks ($P = 0.67$). The 50% fusion rate in the ICBG + OF-HF group may be due to the sample size used in the study, with a difference of fusion in one animal producing the observed results, however a 50% fusion rate is common in this investigator's experience when this model is used correctly, ie, decortication of the transverse processes without decortication of the lamina or body in the gutter.[7,35,37-40] The 40% fusion rate in the ICBG group at 4 weeks likely reflects the inherent osteogenic capabilities of the iliac crest graft,[1-9] whereas the OF-HF silicate carbonate appetite graft only has osteoconductive[19,41] and osteoinductive properties,[42] requiring additional time to recruit osteogenic precursor cells.

MicroCT Morphometric analysis revealed that the OF-HF group initially had the lowest bone volume at four weeks but exhibited significantly greater bone volume than the ICBG group, and a greater average bone volume than the ICBG + OF-HF group at 12 weeks. This discrepancy is likely, in part, due to the advanced remodeling of bone growth from the ICBG due to having inherent osteogenic properties,[1-9] as well as additional surface area on the silicate carbonate appetite particles.[43] Synthetic grafts often exhibit relative delayed bone growth unless combined with bone marrow aspirate,[44] which the OF-HF graft is capable of such integration. These findings highlight the osteoinductive properties,[22] stable scaffolding,

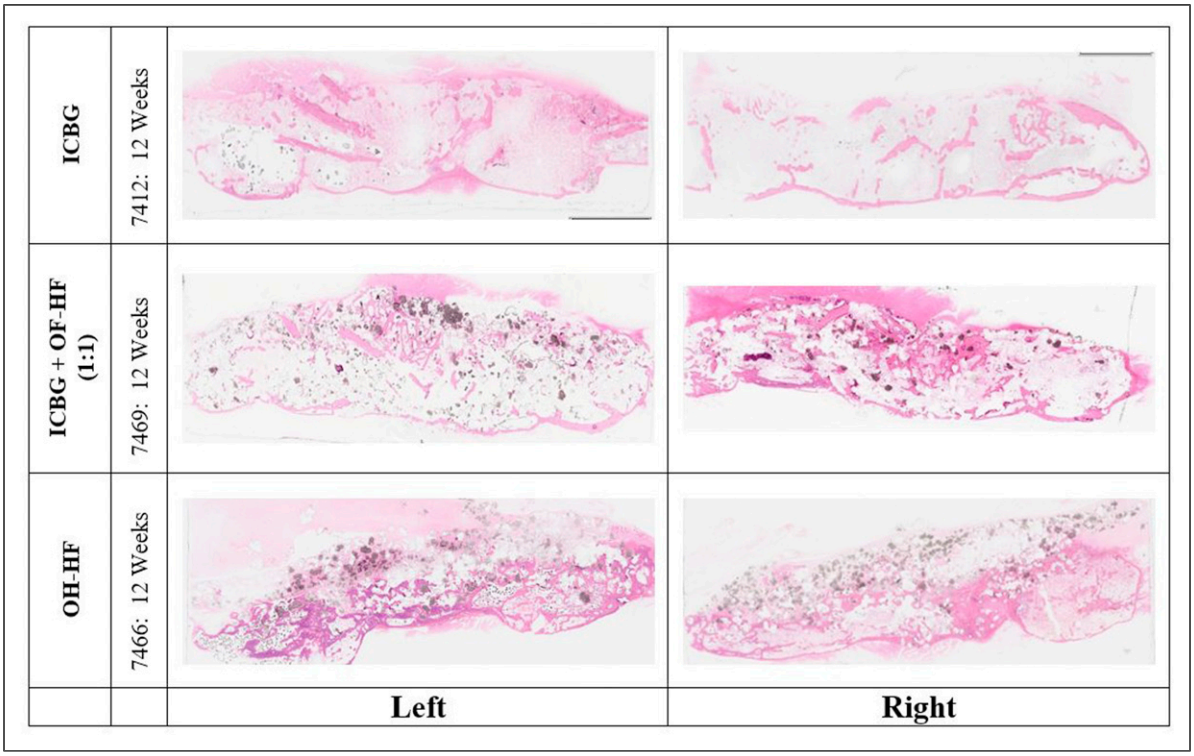

Figure 4. H&E histology images of the fusion masses at 12 weeks

and optimal environment that is provided by the OF-HF graft, fostering a more structurally sound fusion. In addition, OF-HF is hydrophilic and can be used with blood, bone marrow aspirate, or currently available biologics, enhancing the osteogenic capability of OF-HF. The implant volumes observed were consistent with expectations based on the volume of graft implanted during the surgical procedure for each group.

Synthetic bone grafts are widely used in dentistry and orthopedics to promote bone growth and bonding. Silicate ceramics are favorable due to their biocompatibility, strong bonding to surrounding tissue to promote integration and prevent migration,[22] osteoinductive properties supporting bone regeneration,[42] and controlled resorption rate to serve as a continuous scaffold for sustained structural support.[20] Additionally, silicate carbonate apatite exhibits inherent antibacterial and antimicrobial properties, reducing the risk of infection.[45]

Other synthetic implants possessing osteoinductive and osteoconductive properties have shown similar fusion rates to ICBG.[46-48] In a review of 12 clinical studies, bioactive glass demonstrated an 89.6% fusion rate when used as a bone graft extender, compared to 91.6% with ICBG alone.[47] In another clinical model, a biphasic calcium phosphate graft was shown to yield an 83% one year fusion rate compared to 75% with autograft.[48] In the same model, another synthetic graft composed of calcium triphosphate produced a fusion rate of 89%.[48] These results show grafts possessing osteoinductive and osteoconductive properties can achieve fusion rates similar to those of autograft alone.

A strength of this study is that it adhered to ASTM guideline F2884-12, which outlines the required testing of bone graft substitutes in the spine for FDA approval. Additionally, all surgeries and animal housing were conducted at a single center, with one surgeon performing every procedure. A limitation of this study model includes the furthest timepoint being 12 weeks because fusion rates and graft resorption could be further elucidated from a 26-week timeframe, but this knowledge does not increase fusion rate in this model.[24,25] Additionally, although a power analysis was performed to adequately power the study to detect a 20% difference in outcomes, a sample size of 10 animals at the final timepoint is a limiting factor, where a difference in a single animal can result in an apparent 10% difference in fusion rate.

The OF-HF graft incorporates these favorable aspects of silicate carbonate apatite into an FDA-cleared autograft equivalent, infused with collagen to promote improved handling, moldability, and structural scaffolding, while preventing migration. OF-HF was interpreted to exhibit favorable biocompatibility with no evidence of adverse effects/pathology (eg, exuberant inflammation or fibrosis, necrosis, degeneration), locally or systemically, which was comparable to that observed with the ICBG. In addition, OF-HF exhibited no evidence of adverse effects on treatment site osteogenesis/bone bridging, the magnitude and incidence of which were increased over time relative to the ICBG Positive Control.

The comparable fusion rates in stand-alone use and as an autograft extender, combined with the significantly increased bone volume in both groups at the 12-week interval demonstrates through this animal study the OsteoFlo Hydro-Fiber™ graft is a non-inferior alternative to autograft in stand-alone use or as an autograft extender.

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