David D. Hile
Frank Kandziora
Kai-Uwe Lewandrowski
Stephen A. Doherty
Michael P. Kowaleski
Debra J. Trantolo

A poly(propylene glycol-co-fumaric acid) based bone graft extender for lumbar spinal fusion: in vivo assessment in a rabbit model

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D. D. Hile (✉) · S. A. Doherty
D. J. Trantolo
Cambridge Scientific Inc., Cambridge,
MA, USA
E-mail: hiledd@yahoo.com
Tel.: +1-617-5762663
Fax: +1-617-5472663

F. Kandziora
Charité—Universitätsmedizin, Berlin,
Germany

K.-U. Lewandrowski
Cleveland Clinic Foundation,
Cleveland, OH, USA

M. P. Kowaleski
Tufts University School of Veterinary
Medicine, North Grafton, MA, USA

Abstract *Study design:* An animal model of posterolateral intertransverse process lumbar spinal fusion compared fusion rates amongst autologous bone (group 1), a porous, bioabsorbable, scaffold based on the biopolymer, poly(propylene glycol-co-fumaric acid) (PPF) (group 2), and a combination of autograft and the bioabsorbable scaffold (group 3). *Objectives:* To evaluate the feasibility of augmenting spinal fusion with an osteoconductive and bioabsorbable scaffold as an alternative or as an adjunct, i.e., an extender, to autograft. *Summary of background data:* There is little preclinical data on applications of bioabsorbable bone graft extenders in spinal fusion. *Methods:* New Zealand White rabbits underwent single-level lumbar posterolateral intertransverse process fusion. Animals were treated with one of three materials: autologous bone (group

1), a bioabsorbable material based on PPF (group 2), and the PPF biopolymer scaffold with autologous bone graft (group 3). Animals were evaluated at 6 weeks, and fusion was evaluated by manual palpation, and radiographic, histologic, and histomorphometric analyses. *Results:* Radiographic and manual palpation showed evidence of fusion in all three groups. Histomorphometric measurement of bone ingrowth showed the highest quantity of new bone in group 3 (91%), followed by group 1 (72%) and group 2 (53%). *Conclusions:* Results of this study suggested that osteoconductive bioabsorbable scaffolds prepared from PPF might be used as an autograft extender when applied as an adjunct to spinal fusion.

Keywords Spinal fusion · Bone graft extender · Bioabsorbable scaffold

Introduction

Clinical spinal fusion procedures are often performed with use of interbody fusion devices and segmented pedicle screw systems [8, 21, 22]. These devices provide structural support until bony union begins. New bone formation has been stimulated by the inclusion of bone graft, such as morselized autograft and allograft [2, 20, 22]. In order to reduce the need for bone graft, bone graft substitutes, specifically bone growth factors stemming from the family of the bone morphogenetic

proteins [1, 3, 5, 13, 15] have been developed as an adjunct to spinal instrumentation. The use of adjunct materials has focused on biologic outcomes associated with new bone formation in support of fusion rather than structural complements to interbody fusion devices.

A previous study evaluated fixation of lumbar vertebrae ex vivo using cages augmented with an injectable material that cures into a rigid scaffold in situ based on the bioabsorbable polymer, poly(propylene glycol-co-fumaric acid) (PPF) [14]. The stiffness

and failure load of cadaveric L4 and L5 motion segments treated with different devices was used to assess fixation. Stabilization provided by bioabsorbable cages, constructed from polylactide, with and without augmentation with the PPF scaffold was compared to allograft and metallic cages of similar design and shape. An approximate 50% increase in stiffness was measured when the bioabsorbable cage was augmented with the PPF scaffold. The study indicated that additional augmentation of biodegradable cages with the PPF scaffold significantly improved mechanical characteristics of the immobilized segment by filling the entire intervertebral space with a supportive matrix through and around the cage.

Although the PPF material has been tested in vivo in a variety of preclinical applications that demonstrated its functional use as either a bone graft substitute or bone graft extender [7, 16–19], no data is currently available on its ability to facilitate spinal fusion. Preliminary studies have shown that the PPF material is osteoconductive through the addition of hydroxyapatite (HA) as a filler. Furthermore, pores are generated in situ by the incorporation of effervescent agents that produce carbon dioxide during the curing process. The porosity and osteoconductivity of the matrix support bone cell migration and proliferation within the PPF scaffold. Curing of the PPF material is induced by a minimally exothermic crosslinking reaction between PPF and vinyl pyrrolidone, and the material sets into a rigid scaffold within approximately 5 min. The compressive strength (5 MPa) and modulus (100 MPa) of the cured scaffold are comparable to cancellous bone [10]. The purpose of the current study was to investigate the feasibility of using a porous, bioabsorbable scaffold to facilitate spinal fusion. Therefore, the effect of the biopolymer PPF on spinal fusion was investigated in this pilot study using an in vivo lumbar posterolateral intertransverse fusion model. The rabbit lumbar intertransverse process fusion model was selected for this feasibility study because it has been well characterized for evaluation of bone graft materials [4, 6].

Materials and methods

PPF scaffold formulation

The PPF-based material consisted of a two-part formulation prepared by mixing solid powder and liquid components with formulations shown in Table 1. The material was prepared by mixing an aqueous solution of crosslinker, 1-vinyl-2-pyrrolidinone (VP; 46% w/w), and accelerator, *N-N*-dimethyl-*p*-toluidine (DMPT; 0.2% w/w) with a dry powdered mixture of the PPF polymer (71.8% w/w) and hydroxyapatite (HA; CAM Implants, Leiden, The Netherlands; 21.6% w/w) to form a viscous

Table 1 Composition of PPF-based scaffold

Chemical	Amount (% w/w)
Solid components	
Poly(propylene glycol-co-fumaric acid) (PPF)	71.8
Hydroxyapatite (HA)	21.6
Benzoyl peroxide (BP)	3.6
Sodium bicarbonate (SB)	1.7
Citric acid (CA)	1.3
Liquid components	
1-Vinyl-2 pyrrolidone (VP)	46.0
Water	53.8
<i>N-N</i> -dimethyl- <i>p</i> -toluidine (DMPT)	0.2

paste. The weight ratio of PPF/VP was kept constant at 8:3. The crosslinking reaction between PPF and VP was initiated by the addition of benzoyl peroxide (BP; 3.6% w/w). Free radical generation was accelerated using DMPT in the liquid mixture. Sodium bicarbonate (SB) (1.7% w/w) and citric acid (CA) (1.3% w/w) were also added to the dry powder formulation. Upon mixing the VP solution and PPF solids, the reaction of the effervescent agents CA and SB resulted in expansion of the PPF scaffold with respective pore sizes of 50–500 μm upon cure with an average pore diameter of $170 \pm 100 \mu\text{m}$ (Fig. 1). Pore diameters were characterized from scanning electron micrographs with the use of Scion Image for Windows, Release Beta 4.0.2.

In vivo evaluation model

The test materials were evaluated in vivo. Principles of laboratory animal care (NIH publication No. 86-23, revised 1985) were followed. Posterolateral intertransverse process spinal fusions (PLSF) were performed in New Zealand White rabbits (4.5–5.0 kg) at the L5 and L6 levels [6, 11, 23, 25]. Transverse processes were exposed via a bilateral paraspinous muscle splitting technique and decorticated using a round 3-mm bur (Micropower Drill, Walter Lorenz Surgical Inc., Jacksonville, FL, USA). The test implant materials were placed across the decorticated processes of six animals per experimental group. These implants consisted of approximately 3 mL of autograft (group 1), the 3 mL PPF scaffold alone (group 2), or 3 mL of a 50:50 mixture (v/v) of autograft and PPF scaffold (group 3). Autograft was collected from the iliac crest and morselized prior to re-implantation. Morselized autograft and PPF scaffold were mixed in a sterile bowl and then implanted. The implants were placed and fixed by closing the fascial layers with interrupted sutures. All animals were sacrificed 6 weeks postoperatively, and the experimental segments were harvested, leaving the surrounding soft tissues intact.

Fig. 1 Scanning electron micrograph of the cured PPF material. Diameters of the pores ranged between 50 and 500 μm , and the average pore size was approximately 170 μm

Manual palpation

Fusion was evaluated following harvest by manual palpation [6]. Segments were graded as either fused (no segment motion during palpation) or non-fused (segment motion). The fusion mass was evaluated independently on each side, but successful fusion was only inferred when both sides were found to consist of a contiguous fusion mass. Two investigators conducted the palpation evaluation independently and only those segments graded as fused by both investigators were considered a successful fusion.

Radiographic evaluation

Following explantation, radiographs were obtained in the anteroposterior plane using a specimen X-ray unit (Microfocus 50E6310F/G; Xerox, Rochester, NY, USA). Radiographs were taken at minimal exposure (32 kvp, 2 s) using film (Cronex Microvision, Dupont Medical Products, Wilmington, DE, USA), cassettes (MR Detail; AGFA Richfield Park, NJ, USA) and screens (Mammoray, AGFA). Fusion was inferred to be complete when observing a contiguous fusion mass between adjacent transverse processes. Successful fusion was only inferred when observing a contiguous fusion mass bilaterally. The number of segments displaying a contiguous fusion mass within the experimental treatment groups was defined as the *Radiographic Fusion Index*.

Histologic and histomorphometric evaluation

Explanted, specimens were fixed in 10% buffered formalin. Following radiographic analysis, soft tissue was

gradually removed from the specimens to reveal the bone segments of the vertebrae and transverse processes including the fusion mass. Segments containing the fusion mass were decalcified in 4 N formic acid and then embedded in paraffin. Serial longitudinal sections 4–6 μm thick at 50- μm intervals were cut in the coronal plane such that the two fused, adjacent transverse processes would be shown in one histologic slide. The sections were stained with haematoxylin-eosin (H&E). Slides were examined for continuous bony trabeculae connecting the two adjacent L5 and L6 transverse processes. In addition, slides were analyzed for the presence of fibrous tissue, inflammatory cells and multinucleated giant cells within the fusion mass and adjacent tissues.

The slides were also used for histomorphometric evaluation of new bone formation in response to the fusion procedure and implantation of the PPF repair material. Quantitative evaluation of bone repair within the fusion mass was performed by acquiring images of serial longitudinal sections of the specimen using a Spot Insight CCD video camera system (Diagnostics Instruments Inc., Sterling Heights, MI, USA) that was mounted on a Nikon Eclipse E600 microscope. Images were digitized and analyzed using Image Pro Plus software. The areas occupied by new bone in the fusion area between the L5 and L6 transverse process were quantified using H&E-stained slides based on six animals per group. The fusion area was defined as the area between the transverse processes containing the graft material and exclusive of the transverse process. The fusion mass was semiquantitatively evaluated by measuring new bone formation, expressed as a percentage of the area of the fusion mass compared to the entire area between the L5 and L6 transverse process. This ratio was calculated for each sample using an average of six templates, or

region of interest masks, placed in six areas across the fusion site. The parameter, defined as the *Histomorphometric Fusion Index*, is reported as a percentage rate and is expressed as a mean $\pm$ SD.

Statistical analysis

Comparison of histomorphometric parameters of spinal fusion was performed using the Wilcoxon Sum-of-Ranks test. Statistically significant differences were defined at a 95% confidence level, corresponding to a p-value of 0.008 using Bonferroni's correction. The values are given as mean $\pm$ SD.

Results

There were no postoperative complications at any of the implant sites. No deep infections were observed over the entire postoperative period. Specimens were inspected macroscopically after having been dissected, and prior to sectioning and embedding for histologic, and histomorphometric analysis. All fused segments were retrieved intact, except for one animal treated with autograft in which the fusion mass separated during explantation. Because the fusion mass had not been examined prior to removal and it was not clear whether the failure was due to technician error or failure of fusion; this sample was omitted from the study.

All experimental specimens were manually inspected for fusion. The analyses suggested that successful fusion was achieved in 2/5 of animals treated with autograft, 3/6 of animals treated with the PPF alone, 4/6 of animals treated with autograft augmented with the PPF (Table 2). There was no macroscopic granulation tissue present in any of the retrieved samples between the L5 and L6 transverse processes following implantation of the PPF material. All surgical sites appeared to have healed well and there was no apparent adverse reaction of the surrounding soft tissues to the in situ cured material.

Radiographic studies

Anteroposterior radiographs were made of all specimens after retrieval. The radiographs were reviewed for

evidence of solid fusion. Successful fusion was inferred by the finding of a contiguous fusion mass between adjacent transverse processes. Three of the five specimens treated with autograft were considered fused by radiographic analysis, which was greater than that observed using manual palpation. Radiographs taken of segments treated with PPF, and autograft augmented with PPF demonstrated successful spinal fusion in 3/6, and in 4/6, respectively (Table 2). There were no radiographic lucencies in and around the fusion sites. Representative radiographs from each experimental group are shown in Fig. 2.

Histologic and histomorphometric analysis

Histologic evaluation of the segments treatment with autograft showed new bone formation between the adjacent L5 and L6 transverse processes. New bone formation occurred between the particles of the morselized autologous bone graft with little or no interposition of fibrous tissue. In three of the five samples, there was evidence of continuous bony trabeculae connecting the two adjacent transverse processes (Fig. 3).

Retrieval of the fusion mass obtained when the PPF material was implanted alone indicated that the PPF remained intact. There was new bone formation, which occurred from the exterior to the interior. At 6 weeks postoperatively, the PPF polymer underwent superficial degradation followed by bony ingrowth. In addition, there was some fibrous tissue formation between the PPF implant and the newly formed bone. In three of the six samples, there was evidence of bony trabeculae connecting the two adjacent transverse processes via the PPF material in between. Incomplete fusion was noted in cases where new bone was not prevalent within the PPF material (Fig. 4).

Segments treated with an equal mixture of autograft and PPF material were clearly identifiable during explantation. The porous PPF scaffold was infiltrated throughout with newly formed bone. New bone formation was primarily noted to occur within pores as polymer degradation had yet to substantially occur. The depth of bone ingrowth could not be reliably determined since the autologous bone graft had been mixed with the PPF prior to implantation. No significant inflammatory changes were noted. New bone formation within and around the PPF took place without significant

Table 2 Summary of spinal fusion rates by experimental group

	Manual palpation	Radiographic Fusion Index	Histomorphometric Fusion Index
Group 1 (autograft)	2/5	3/5	72 $\pm$ 12%
Group 2 (PPF)	3/6	3/6	53 $\pm$ 12%
Group 3 (autograft + PPF)	4/6	4/6	91 $\pm$ 17%

Fig. 2 Radiograph of fused segments in animals of **a** autograft, **b** PPF alone and **c** autograft + PPF. **a** Note the narrow appearance of the fusion mass in the autograft group when compared to the other two groups. **b** On plain radiographs, the appearance of the bioabsorbable polymer scaffold is easily distinguishable from newly formed bone at the fusion site. **c** Note the uniform density of the fusion mass versus that in **a** and **b**

Fig. 3 Photomicrograph of the L5 and L6 spinal segment treated with morselized autograft (H&E one time coronal section). The two adjacent transverse processes are shown on either side of the image and are outlined by the dotted line. In between the two transverse processes, there is new bone formation (black arrow) that bridges the two adjacent transverse processes as evidenced by calcified woven bone (inset)

interposition of fibrous tissue. Occasionally, macrophages were present, and these macrophages contained intracellular inclusions of what appeared consistent with polymer. In four of the six samples, there was evidence of continuous bony trabeculae connecting the two adjacent transverse processes (Fig. 5).

Histologic findings were supported by the histomorphometric analysis. By quantitative volume measures (expressed by the *Histomorphometric Fusion Index*), animals fused with autograft augmented with the PPF material ($91 \pm 17\%$) followed by autograft alone ($72 \pm 12\%$) showed the highest amount of new bone formation (Table 2) compared with animals treated with PPF alone ($53 \pm 12\%$). Furthermore, histomorphometric analysis demonstrated that the amount of new bone,

which formed at the implantation sites was significantly higher in the groups that received a combination of the PPF material and autologous bone graft than in the animals who received PPF alone (Table 2; $p=0.002$). Differences in the *Histomorphometric Fusion Index* between the autograft and PPF material only ($p=0.04$) and autograft and autograft augmented with PPF ($p=0.08$) were not statistically significant.

Discussion

The study investigated the feasibility of using a porous bioabsorbable material as an autologous bone graft extender for application in spinal fusion. The

Fig. 4 Photomicrograph of the L5 and L6 spinal segment treated with the PPF material (PPF; H&E one time coronal section). The two adjacent transverse processes are shown on either side of the image and are outlined by the *dotted line*. The PPF material is surrounded by newly formed bone illustrating its osteoconductive properties. Although there is no significant bone growth into the material, there is new bone formation in close proximity to it (*inset*). Fusion is incomplete, as new bone trabeculae do not connect the two transverse processes

Fig. 5 Photomicrograph of the L5 and L6 spinal segment treated with a mixture of morselized autograft and the PPF material (H&E one time coronal section). The two adjacent transverse processes are shown on either side of the image. The mixture of morselized autograft and PPF induced more new bone formation. The PPF material showed good osteointegration (*inset*)

posterolateral intertransverse rabbit spinal fusion model has been established in the literature for the study of the biologic and biomechanical aspects of lumbar spinal fusion using experimental materials. The scope of this study investigated the use of PPF scaffold alone and the PPF material combined with autologous bone graft and compared the spinal fusion process to an autograft control (group 1).

Porous bone repair materials provide a structural construct to enable a more rapid ingrowth of bone cells while stabilizing the defect site [12, 24]. A porous construct with mechanical properties comparable to native bone will initially provide structural support to the defect site. Thereafter, as the implant degrades, the net

result of newly formed bone plus residual implant, the “repair-composite,” is expected to provide continued support to the defect reconstruction, while yielding to the establishment of native bone. A bioabsorbable material for spinal fusion is expected to provide rigid stabilization initially, and enable progressive stress-sharing with the surrounding, healed bone that may prevent osteopenia and/or long-term implant failure.

Results of this rabbit posterolateral spinal fusion study suggested that PPF scaffold might be used as an extender for autologous bone graft. At 6 weeks post-operatively, all surgical sites appeared to have healed well and there was no apparent adverse reaction of the surrounding soft tissues to the in situ cured material.

The PPF material implanted without autograft was surrounded by newly formed bone. Although successful fusion was identified via manual palpation and radiography in a portion of the segments implanted with PPF only (3/6), the presence of a contiguous fusion mass was not consistent. Sections of the fusion mass for histomorphometric analysis were observed to have more bone at the periphery of the implant material than in the interior, and values for the *Histomorphometric Fusion Index* were consistently lower than the other experimental groups containing autograft. Mixing the PPF formulations with cancellous autologous bone graft, and presumably enhancing osteoinductive properties in vivo, increased new bone ingrowth into and between particles of the PPF material. Mixing autograft into the PPF material appeared to increase the fusion mass compared to PPF implanted without the addition of autograft. Moreover, the *Histomorphometric Fusion Index* in the combined autograft and PPF construct was comparable to the use of autograft alone.

Although this study demonstrates the utility of a bioabsorbable bone graft extender in a rabbit spinal fusion model, there are limitations to this study and several issues have yet to be investigated. There are significant differences in spinal fusion rates between humans and non-primates [9]. Therefore, future studies should use a higher order animal model, such as the rhesus monkey. Moreover, the strength of the fusion mass was determined manually at a single time point, and the concurrent effects of bone remodeling and polymer degradation over a longer period of time have yet to be determined for spinal fusion.

Although observations of this study are supportive of the application of a PPF-based scaffold as an extender for autologous bone graft, it cannot be inferred from this study that the spinal fusion process was superior when autograft was mixed with PPF. However, it was not the purpose of this study to determine whether fusion rates are higher with use of PPF. Rather, it was the purpose of this study to establish whether a

bioabsorbable polymer scaffold would lend itself to the facilitation of spinal fusion, particularly when autologous spinal stocks are deficient. Therefore, the statistically insignificant differences between the *Histomorphometric Fusion Index* and results of the manual palpation were expected.

With respect to the biologic function of the PPF scaffold, it would appear ideal if new bone would progressively replace the hydrolyzing PPF biopolymer. If polymer degradation is faster than ingrowth, macroscopic voids and secondary implant breakdown may occur. Prior studies suggest that PPF degradation occurs concurrently with expected bone regeneration [10] and that new bone formation occurs initially within pores of the implant then progressively replaces the scaffold during the concomitant degradation and ingrowth processes [16]. Further studies will be required to assess the temporal affects of PPF degradation on the nature and integrity of the fusion mass.

Although no conclusions about the clinical effectiveness of the PPF material as an autologous bone graft extender can be drawn from this study, the current data suggest that the PPF-based scaffold may be used in conjunction with autologous bone graft to achieve equivalent fusion rates than the use autologous bone alone. The findings of this study may be used to support further investigation of a bioabsorbable bone graft extender for spinal applications with emphasis on the influence of porosity, mechanical strength, and foreign body reaction during polymer degradation on the outcome of spinal fusion procedures.

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