A Rat Dorsal Midline Lumbar Fusion Model for Evaluating Osteoconductive Shape Memory Scaffold-Guided Fusion

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INTRODUCTION: Autograft is the gold standard for spinal fusion, but is limited by donor-site morbidity, patient bone quality, and inconsistent fusion rates. Bone-morphogenic-protein-2 (BMP-2) augmented allografts can improve fusion rates but are associated with significant and sometimes life-threatening inflammatory complications. These limitations support the need for novel and safe fusion strategies capable of reliable bone formation. We previously developed a 3D printed osteoconductive hydroxyapatite–poly(lactic-co-glycolic acid)-*b*-poly(ethylene glycol)-b-poly(lactic-co-glycolic acid) (HA-PELGA) composite (Zhang et al., 2019) as synthetic degradable shape memory bone graft to guide effective long bone regeneration in critical-size rat femoral segmental defects without or with a minimal dose of rhBMP-2. Here we explore the osteoconductive and hydration-induced stiffening behavior of the shape memory HA-PELGA electrospun mesh (Zhang et al., 2017) for spinal fusion applications. We evaluated posterolateral Wiltse vs. dorsal midline approaches in a rat L4-L5 fusion model to establish a reliable surgical model to evaluate the efficacy of HA-PELGA scaffold-guided bony bridging and fusion.

METHODS: PELGA was synthesized by ring-opening polymerization of D,L-lactide and glycolide (8:1 molar ratio) using poly(ethylene glycol) (PEG, Mn = 20 kDa) as a macroinitiator and Sn(II) 2-ethylhexanoate as the catalyst under melt conditions (130 °C, 4 h) under Ar protection (Fig. 1A). The polymer was purified by precipitation and characterized by ^{1}H NMR and gel permeation chromatography (GPC). The HA-PELGA composites (10 or 25 wt% HA) were either solvent-cast into 10 × 3 mm^2 dense films or electrospun into porous mesh as reported.[1] A subgroup of dense 25 wt% HA-PELGA films were fragmented to mimic morselized autograft. All scaffolds were UV-sterilized prior to surgical uses. All animal procedures were approved by institutional IACUC. Male Sprague-Dawley rats (10-12 wk) were used to reduce variability in skeleton size. For the posterolateral Wiltse approach (Fig. 2A), a midline skin incision was made over the spinous processes from L4-L5. Bilateral paramedian facial incisions were made to expose the L4–5 transverse processes and decorticated with a surgical scalpel or a high speed burr. Sterile 25%wtHA-PELGA fragments were padded into the fusion bed. For the dorsal midline approach, a single skin incision was made over the L4–L5 spinous processes. Erector spinae musculature was sharply and bluntly dissected and elevated bilaterally to expose the posterior elements at the L4 and L5 levels. A high-speed cylindrical burr was utilized to decorticate the posterior elements from the base of the L5 transverse process across the lamina and facet complex of L4–L5 to the base of the L4 transverse process. Decortication proceeded until punctate bleeding was observed. A sterile 25%wtHA-PELGA dense film or 10wt%HA-PELGA electrospun mesh was positioned directly over the decorticated bone surface. This process was repeated bilaterally. Micro-CT was performed on post-op day 3, week 2 and week 4 to monitor fusion.

RESULTS: ^{1}H NMR of PELGA revealed a degree of polymerization (DP) of 695 or number average molecular weight (Mn) of 118 kDa, with a lactide:glycolide ratio of 8.1:1, closely matching theoretical values (Figure 1B). GPC revealed a monomodal distribution with Mn = 92.5 kDa and PDI (Đ) = 1.20 (Figure 1C). The posterolateral Wiltse approach provided limited visualization of the target fusion bed, led to inconsistent scaffold placement and contact with cortical bone, and did not allow for adequate leveraging of soft tissues to prevent scaffold migration post-op (Fig. 2B, left). Additionally, both manual and high-speed burr decortication proved challenging and unreliable through this narrow soft tissue interval, resulting in inconsistent decortication of the target fusion bed (Fig. 2B, right). The dorsal midline exposure markedly improved visualization of the posterior elements, facilitated targeted decortication, and provided a better soft-tissue envelope that could be re-approximated to hold the scaffold against the decorticated surface, improving in-situ scaffold stability (Fig. 2C). Initial use of the scaffold in a fragmented format, intended to approximate morselized autograft, led to significant scaffold positional variability. The un-fragmented dense film and electrospun mesh were then evaluated, with the latter exhibiting improved handling, with its hydration-induced stiffening upon contact with biological fluids enabling its contouring to the fusion bed and allowing for reliable cortical contact. Micro-CT at 2 and 4 weeks showed mesh-guided posterior bone bridging across L4–L5 in rats who underwent the optimized dorsal midline exposure (Fig. 2C).

DISCUSSION: Our data show that methodologic refinement of both synthetic graft formats and surgical approaches are key to fusion outcomes. Our evaluations revealed that the Wiltse approach with fragmented HA-PELGA yielded unstable scaffold positioning and inconsistent contact with the fusion bed. Switching to a dorsal midline exposure improved access and visualization, enabling reproducible decortication, more reliable scaffold placement, and the soft tissue closure be leveraged to maintain scaffold-cortical interface. An electrospun HA-PELGA mesh further improved handling, conformity, and stability of scaffold placement. This optimized workflow provides a reproducible and favorable biologic environment to evaluate pre-clinical models of biomaterial scaffolds and biologics for lumbar fusion. Endpoint histological analyses and longitudinal comparisons of the fusion enabled by HA-PELGA mesh with/without a minimal dose of rhBMP-2 vs. Infuse® control are underway.

SIGNIFICANCE / CLINICAL RELEVANCE: This rat lumbar fusion model provides a reproducible platform for evaluating novel scaffolds/biologics. The promising HA-PELGA-guided fusion achieved without rhBMP-2 could potentially reduce reliance on autografts or high-dose rhBMP-augmented allografts.

REFERENCES:[1]Zhang B, Skelly JD, Maalouf JR, Ayers DC and Song J. Sci. Transl. Med. 2019; eaau7411. [2] Zhang B, Filion TM, Kutikov AB and Song J. Adv. Funct. Mater. 2017; 1604784.

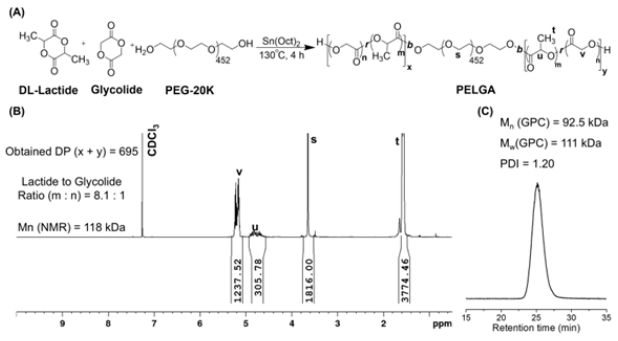

Figure 1: (A) Scheme for synthesis of PELGA, (B) ^{1}H NMR of PELGA in $CDCl_3$, (C) GPC chromatogram of PELGA

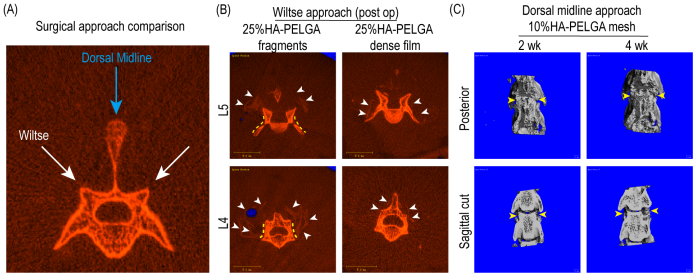

Figure 2: (A) Wiltse vs. dorsal midline approaches. (B) Post-op microCT images showing that Wiltse approach led to inconsistent placement of fragmented or intact film of 25%HA-PELGA (white arrows) relative to fusion beds. (C) Micro-CT images of L4-L5 fusion at 2 and 4 weeks guided by 10%HA-PELGA mesh using the dorsal midline approach (arrows denote fusion mass).