Efficacy of Poly(D,L-Lactic Acid-co-Glycolic acid)-Poly(Ethylene Glycol)-Poly(D,L-Lactic Acid-co-Glycolic Acid) Thermogel As a Barrier to Prevent Spinal Epidural Fibrosis in a Postlaminectomy Rat Model

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**Study Design:** Experimental animal study.

**Objective:** The authors conducted a study to determine the efficacy and safety of the PLGA-PEG-PLGA thermogel to prevent peridural fibrosis in an adult rat laminectomy model.

**Summary of Background Data:** Peridural fibrosis often occurs after spinal laminectomy. It might cause persistent back and/or leg pain postoperatively and make a reoperation more difficult and dangerous. Various materials have been used to prevent epidural fibrosis, but only limited success has been achieved.

**Methods:** The PLGA-PEG-PLGA thermogel was synthesized by us. Total L3 laminectomies were performed in 24 rats. The PLGA-PEG-PLGA thermogel or chitosan gel (a positive control group) was applied to the operative sites in a blinded fashion. In the control group, the L-3 laminectomy was performed and the defect was irrigated with the NS solution 3 times. All the rats were killed 4 weeks after surgery.

**Results:** The cytotoxicity of this thermogel was evaluated in vitro and the result demonstrated that no evidence of cytotoxicity was observed. The extent of epidural fibrosis, the area of epidural fibrosis, the density of fibroblasts and blood vessel were evaluated histologically. There were statistical differences among the PLGA-PEG-PLGA thermogel or chitosan gel group compared with the control group. Although there was no difference between the PLGA-PEG-PLGA thermogel and chitosan gel, the efficiency of the PLGA-PEG-PLGA thermogel showed slightly improved comparing with the chitosan gel.

**Conclusions:** The biocompatibility of the PLGA-PEG-PLGA thermogel was proved well. The application of this thermogel effectively reduced epidural scarring, and prevented the subsequent adhesion to the dura mater with improved results comparing with the chitosan gel. No side effects were noted in all the rats.

**Keywords:** epidural fibrosis; thermogel; laminectomy; postoperative adhesion; scar tissue

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Intruduction

Failed back surgery syndrome (FBSS), occurring at a rate of 5%–40% postoperatively,\(^1,2\) is characterized by the recurrence of persistent back and/or leg pain after one or more surgical procedure aimed at healing the lumbar-sacral diseases.\(^3\) This syndrome can results from inadequate surgical decompression, recurrent disc herniation, lumbar instability, facet joint disease, permanent nerve root damage, epidural fibrosis, or arachnoiditis.\(^4,5\) However, epidural fibrosis has been reported to occur in 8%-14% patients undergoing spinal surgeries,\(^1,6\) and it is supposed to be the underlying cause of postoperative pain.\(^7\) The epidural fibrosis can lead to extradural compression or nerve root traction which can cause impaired axoplasmic transport and restricted arterial supply, resulting in painful radiculopathy.\(^1,8-11\) What’s more, the tenacious scar tissue increases the challenges in subsequent spinal exposure procedures technically by adding to risks of nerve root lesion and dural tear.\(^12,13\) Therefore, a variety of technologies and materials were carried out to prevent the scar formation.

Minimal invasion to the spinal canal is considered as the primary measure to reduce the epidural fibrosis. Although microsurgical techniques and improvements in bipolar coagulation are introduced, both of which reduce the incidence of tissue trauma, epidural fibrosis after spinal surgery still occurs.\(^14\)

As for materials, according to their physical condition, they can be classified as solid,\(^15,16\) liquid,\(^17\) gel,\(^18\) membrane,\(^19\) materials and so on. However, the research results are inconsistent\(^18-21\) and there is no clinically adopted treatment protocol to prevent epidural fibrosis.

An ideal material for prevention of epidural scarring adhesion should be a sort of viscous semifluid material without risk of neurologic compression, which would allow it be injected easily and fill the irregular laminectomy defect. What’s more, excellent biocompatibility and absorbability during the wound healing period would be of great importance to minimize serious foreign body reaction and inflammatory response.

Hydrogels are hydrophilic polymer networks that can hold a large amount of water and maintain a 3-dimensional structure, and they have been widely investigated.
in biomedical applications.\textsuperscript{22, 23} In the last decade, thermogelling polymers that undergo a reversible sol-gel transition in water upon temperature changes have attracted a lot of attention for use as injectable biomaterials.\textsuperscript{24-28} The advantages of these materials include good biocompatibility, easy administration, avoidance of organic solvents, and facile sterilization via filtration.

Biodegradable thermogels that consist of PEG and aliphatic polyester are particularly important and interesting. These building blocks have been approved by the US Food and Drug Administration (FDA) and used in humans. Meanwhile, the synthetic procedure for constructing PEG/polyester copolymers demonstrates excellent repeatability.\textsuperscript{29-31} Moreover, their gel properties and in vivo persistence in gel form can be well-modulated via many molecular parameters, such as molecular weight (MW),\textsuperscript{29, 32} block ratio,\textsuperscript{29, 33, 34} and even end group\textsuperscript{35, 36} in order to satisfy practical requirements. Recently, our group also suggested that the thermogels composed of PEG and poly(D,L-lactic acid-co-glycolic acid) (PLGA)/ poly (ε-caprolactone-co-D,L-lactic acid) (PCLA) could serve as effective barrier devices to prevent postoperative abdominal adhesion.\textsuperscript{37, 38} Even so, to the best of our knowledge, no such a sort of thermogel systems have been employed in an attempt to prevent peridural fibrosis after spinal laminectomy.

Herein, the thermogelling PLGA-PEG-PLGA triblock copolymer was synthesized in the present study, and the efficacy and safety of the PLGA-PEG-PLGA thermogel to prevent peridural fibrosis in an adult rat laminectomy model were evaluated. The results, comparing with a novel adhesion barrier chitosan(CHS) which was investigated with satisfactory results for preventing epidural fibrosis recently, were examined via gross anatomical observations and histological examinations.

**Materials and methods**

**Animal Population**

Twenty-four male Sprague-Dawley (SD) rats (body weight = 375 ± 25 g) were provided by the department of laboratory animal science of Fudan University. All
animal experiments were conducted in accordance with the protocol approved by the Animal Care and Use Committee of Zhongshan Hospital, Fudan University.

**Synthesis of The PLGA-PEG-PLGA Triblock Copolymer**

PLGA-PEG-PLGA triblock copolymer was synthesized via ring-opening copolymerization of D,L-lactide (LA) and glycolide (GA) in the presence of Poly(Ethylene Glycol) (PEG) and stannous octoate. The detailed procedure was described in our previously published study. 39

**In Vitro Cytotoxicity Assay**

The CCK-8 assay was used to estimate the cytotoxicity of the synthesized polymer against NIH-3T3 fibroblast cells. Cells (5000 cells/well) were seeded in a 96-well plate containing 100 μL high-glucose medium (H-DMEM, 10% FBS, 50 U/mL penicillin, and 50 U/mL streptomycin) per well and incubated in a CO₂ incubator (37°C; 5% CO₂) for 24 h. Then, 100 μL PLGA-PEG-PLGA or sodium dodecyl sulfate (SDS) in H-DMEM medium with a given concentration was added into the 96-well plate. After 24 h of incubation in the CO₂ incubator, the H-DMEM medium in each well was replaced with 200 μL fresh H-DMEM medium, and 20 μL CCK-8 was added to each well. Cells were cultured under the same CO₂ atmosphere for another 3 h. The absorbance of each sample was tested at 450 nm using an enzyme-labeled instrument (Multiscan MK3; Thermo). Cytotoxicity was defined by the relative viability (100% viability was defined by the H-DMEM media without extra materials).

**Surgical Procedure**

An adult rat laminectomy model 40, 41 was used to assess the efficacy of the PLGA-PEG-PLGA thermogel to prevent epidural scarring. After general anesthesia was induced, the dorsal hairs around L2–L4 were shaved and the surgical field was sterilized using povidone-iodine. Next, a midline skin incision was made, and the paravertebral muscles were opened. Then, total L3 laminectomy was performed and the
dura mater was left intact. An approximately 5×3 mm² laminectomy defect was established.

Once the laminectomy defect was achieved, rats were randomly divided into three groups (8 rats/group). In the PLGA-PEG-PLGA thermogel-treated group, the aqueous polymer solution was transferred into the exposed epidural space and around the freed nerve roots. The thermogel rapidly formed (about 30 s) at the administration site after contacting the warmer surrounding tissues. The amount of thermogel administered to each animal was 0.1 mL, which was sufficient to totally fill the epidural space. In the CHS gel-treated group, the same amount of CHS gel was applied in each rat. In the control group, the epidural space was only irrigated 3 times using the NS solution. The wound was closed in layers, and no other medical treatments were used. The rats were separately housed during the postoperative period, and 4 weeks later they were euthanized by intraperitoneal pentobarbital injection (150 mg/kg).

Clinical Observations

Postoperative recovery conditions, including the rat’s general state, evidence of infection and hindlimb function was observed in all the rats. The hindlimb function was evaluated by the method Song et al. had described. Meanwhile, animals whose nerve roots were injured during surgery were excluded from all following studies.

Evaluation of Epidural Scarring

Four weeks after surgery, one rat in each group was randomly selected and euthanized. The examinations of laminectomy site were performed qualitatively, including inflammatory responses in surrounding tissues, difficulty of re-exposing the dura mater, the amount of new bone, and epidural fibrosis. All specimens were evaluated by a surgeon blind to the study protocol. The remaining rats of each group underwent histological evaluation. After the euthanasia was achieved, the whole spinal columns, including the surrounding muscle tissues, were resected from L2–L4, fixed in 4% formalin for 1 week, and decalcified by ethylenediamine tetraacetic acid (EDTA).
for 8 weeks. Finally, only the L3 vertebra was reserved, dehydrated, and embedded in paraffin. Two successive transversal sections were made in the middle of L3 and stained with hematoxylin and eosin (HE) and Masson’s trichrome dye. All relevant procedures were performed at room temperature.

All sections were evaluated by a blinded pathologist microscopically. Sections stained with hematoxylin and eosin were examined for the extent of adhesion, the density of the fibroblasts and the blood vessels. The extent of adhesion was assessed according to the semiquantitative classification described by He, et al.\textsuperscript{41} as follows: grade 0, dura mater is free of scar tissue; grade 1, only thin fibrous bands are observed between the scar tissue and dura mater; grade 2, continuous adherence is observed in less than two-thirds of the laminectomy defect; and grade 3, scar tissue adherence is large, affecting more than two-thirds of the laminectomy defect, or the adherence extended to the nerve roots. Three 2500 μm\textsuperscript{2} vascularized fields in each section were used to analyze blood vessel density. The number of blood vessels was counted in each field, and then the average vessel density of each section was calculated. Meanwhile, the density of fibroblasts was similarly counted in the corresponding fields. The sections stained with Masson’s trichrome were used to evaluate the area of fibrosis between the paraspinal muscles and dura mater, which were recorded using Image-Pro Plus 6.0 software. All sections were measured 3 times, and the average area was determined.

All the data were statistically analyzed using SPSS software (version 17.0). The non-parametric Mann–Whitney U test was employed for the extent of adhesion. And One-Way ANOVA and the LSD test were used to analyze the area of fibrosis, the fibroblast density, and the blood vessel density. In this study, $p < 0.05$ is considered statistically significant.

**Results**

**In Vitro Cytotoxicity of the PLGA-PEG-PLGA Triblock Copolymer**

To assess the biocompatibility of the PLGA-PEG-PLGA triblock copolymer, in vitro cytotoxicity testing was performed on NIH-3T3 fibroblast cells. Cell viability was
compared to the control group in which cells were cultured in H-DMEM medium without any other materials (100% viability). As for PLGA-PEG-PLGA triblock copolymer, NIH-3T3 cell viability was close to 100% at all concentrations. In contrast, cell viability in the presence of SDS was almost 0% while the SDS concentration increased up to 0.1 mg/mL. From these results, we could infer that the PLGA-PEG-PLGA triblock copolymer has good biocompatibility and is suitable for use as an implantable biomaterial.

Clinical Observation

All incisions healed within 1 week, and no infections were detected throughout the experimental period. The function of the hindlimbs in one rat in the control group was influenced by laminectomy with the posture of Grade 1 (important deformation) and the force of Grade 2 (hindlimb can be moved horizontally but cannot support the body weight). This rat was excluded. All the other animals were healthy and ambulatory until the end of follow-up.

Macroscopic Observation of Specimens

One month after surgery, animals were sacrificed and the necropsies were performed. No serious inflammatory responses were observed at the laminectomy sites or the surrounding soft tissues. Membranaceous epidural scar tissues in the PLGA-PEG-PLGA thermogel-treated group and funiform epidural scar tissues in the CHS gel-treated group were observed. Meanwhile, only a small amount of new bone had regenerated. Furthermore, it was easy to separate the scar tissues from the dural mater and re-expose the dural sac in both groups (Figure.2). In contrast, the control group suffered from severe epidural scar adhesions, and these thick, dense adhesions made re-exposure of the dura mater very difficult.

Histological Evaluation of Epidural Fibrosis
1) The Semi-Quantitative Evaluation of Epidural Fibrosis

In terms of the extent of epidural fibrosis, both Thermogel and CHS gel groups were dominated by Grade 1, while Grade 3 was the main rating in the control group (Table.1). There were statistically significant differences between the CHS (p<0.05) and PLGA (p<0.05) group comparing with the control group separately. Although there was no statistically significant difference between the CHS group and PLGA group (p>0.05), Grade 1 was observed in 6 (86%) of the animals in thermogel group, which was more than 5 (71%) of the animals in the CHS group. The histologic view is shown in Fig. 3.

2) The Quantitative Assessment of Epidural Fibrosis

The area of epidural fibrosis, density of fibroblasts and blood vessel were quantitatively evaluated. Compared with the control group, the area of epidural fibrosis in the PLGA-PEG-PLGA thermogel or CHS gel group was significantly reduced 4 weeks after surgery (Figure.4A). This feature suggested that the administration of the PLGA-PEG-PLGA thermogel or CHS gel remarkably decreased the amount of collagen fibers, which is secreted by fibroblasts. Also, the density of fibroblasts in the PLGA-PEG-PLGA thermogel-treated group and CHS gel-treated group significantly decreased in comparison with the control group (Figure.4B), indicating that the migration of fibroblasts was obviously inhibited by the two gels. Furthermore, both PLGA-PEG-PLGA thermogel and CHS gel significantly decreased blood vessel density, and the results were statistically different from the control group (Figure.4C). This finding could be attributed to the reduction of the postoperative bleeding via the use of PLGA-PEG-PLGA thermogel or CHS gel. Although no significant differences were observed between the PLGA-PEG-PLGA thermogel and CHS gel groups, the efficacy of PLGA-PEG-PLGA thermogel seemed improved comparing with the CHS.

Discussion

Epidural fibrosis is always initiated by the invasion of the epidural space caused
by laminectomy or discectomy.\textsuperscript{43} It has already been experimentally demonstrated that epidural fibrosis is attributed to three main factors:\textsuperscript{21} 1) the destruction of epidural fat; 2) the formation of epidural hematoma; and 3) the migration of fibroblasts from the perivertebral muscles into the laminectomy defect. Therefore, any available materials that can eliminate the abovementioned risk factors—but not impair tissue healing—could reduce the extent of epidural scarring and thus limit the epidural adhesion effectively.

In the past decades, numerous reagents and materials have been used to prevent or limit the formation of peridural fibrosis in animal models and a few human cases.\textsuperscript{19, 44-53} However, most of the strategies demonstrated limiting success. Gels, including ADCON-L,\textsuperscript{20} sodium hyaluronate,\textsuperscript{54} Gel Amidon Oxyd,\textsuperscript{45} high-molecular –weight hyaluronan,\textsuperscript{55} DuraSeal Xact,\textsuperscript{18} Seprafilm Adhesion Barrier\textsuperscript{20} et al., were investigated as promising adhesion-preventing devices. Among them, ADCON-L was an attention-drawing and controversial biomaterial. ADCON-L is a bioresorbable carbohydrate polymer gel which is composed of a polyglycan ester and porcine derived gelatin in phosphate-buffered saline.\textsuperscript{20} In 1997, Stephanie et al.\textsuperscript{46} firstly evaluated ADCON-L as a barrier to inhibit the epidural adhesion on a discectomy and laminectomy model, and the result demonstrated that ADCON-L was effective in significantly reducing peridural adhesion without any adverse effect on the healing process. Additionally, a prospective, multicenter, randomized, double-blind, controlled study of ADCON-L for preventing of epidural fibrosis were conducted in 298 patients and showed that ADCON-L gel could significantly inhibit peridural scar and improve the clinical outcomes without side effect.

However, in 2001, Le et al.\textsuperscript{56} reported that ADCON-L may inhibit dural healing and exacerbate cerebral spinal fluid leak from microscopic durotomies which was not recognized at the time of surgery. Subsequently, Zou et al.\textsuperscript{57} evaluated the effect of ADCON-L gel on spinal fusion via a pig model and finally concluded that ADCON-L gel mixed into autogenous bone graft could decrease bone formation at spinal arthrodesis sites, thus influencing the rate of spinal fusion. Tachycardia and hypotension were also noted by Kalogrianitis et al.\textsuperscript{58} after administration of ADCON-L.
in patients for preventing epidural fibrosis.

Hyaluronic acid (HA) was also under debate for preventing epidural fibrosis. Songer et al. demonstrated a greater reduction in scar formation after laminectomy and discectomy using sodium HA solution treatment with a dog model. However, Hwan-Mo et al. reported that in a 12-week study, HA was absorbed in the late stage resulting in less effective for reducing epidural scarring. Recently, Tsuyoshi et al. evaluated HA gel for preventing epidural fibrosis in a rat model and also demonstrated that HA gel was less effective in reducing epidural fibrosis.

Even though there are various demerits of gels, the trend in preventing epidural adhesion still seems to be following the path of hydrogels, and the administration of a gel into the laminectomy defect as a mechanical barrier between the surgically exposed dura mater and surrounding muscles appears to improve clinical outcomes. Injectable thermogels are also novel good candidates as barrier systems, because their aqueous solutions can easily and thoroughly spread over the epidural cavity and then rapidly form a physical gel as a barrier to prevent the formation of peridural fibrosis after laminectomy according to Songer et al. Recently, some thermogels composed of PEG and biodegradable polyester have been demonstrated to be effective in preventing postsurgical peritoneal adhesion, and the possible mechanisms were also discussed, but to our knowledge, such a system has never been evaluated in spinal surgical procedures before.

Recently, a novel adhesion barrier chitosan gel(CHS), produced from macromolecular polysaccharide and has a structure similar to human tissue, was applied on a rabbit laminectomy model and demonstrated that chitosan was an effective alternative for adhesion barriers.

In this study, we tried PLGA- PEG-PLGA triblock thermogel as a mechanical barrier to prevent the formation of epidural scarring, comparing with the abovementioned CHS. The PLGA- PEG-PLGA triblock copolymer was prepared via ring-opening polymerization. The in vitro CCK-8 assay confirmed that the synthesized polymer had low cytotoxicity (Figure.1), which suggested that the PLGA-PEG-PLGA thermogel is suitable for use as an implantable biomaterial in different biomedical
applications. What’s more, no specific inflammatory reactions were detected in any groups postoperatively, regardless of treatment, and all skin and muscle incisions healed within 1 week postoperation. These findings verified that the thermogel did not cause medically significant adverse effects, although the long-term safety of thermogel applications requires further investigations.

As for the efficacy of preventing epidural fibrosis of the thermogel, gross anatomical observations and histological examinations were performed 1 month after surgery because the first month post-operation is critical to the formation and extent of scarring. Clinical manifestation showed that the liberty of nerve roots was not affected by swelling of the thermogel during gelation, indirectly demonstrating that the swelling of the thermogel was slightly and the thermogel was sufficiently soft without any compression. Gross anatomical observations confirmed the formation of membranaceous epidural scar tissues in the thermogel-treated group (Figure 2) which could scarcely compress the nerve elements. Histological examinations further demonstrated that the extent of epidural fibrosis (Table 1; Figure 3), the area of epidural fibrosis, density of fibroblasts and blood vessel (Figure 4) in the thermogel-treated group were significantly lower in comparison with the control group. This maybe be attributed to the convenience of the administration of the thermogel. Under low temperature (below 37°), this thermogel could be injected under liquid condition, fill the laminectomy area and cover the neurological tissues completely. And soon it would spontaneously transform into gel condition with higher viscosity, fix in the surgery area as a protecting physical barrier in about 30 seconds after contacting with the surrounding tissues. And thus it could completely protect the neurological elements from being adhered and tethered by the scar tissues. The thermogel maybe also could provide a gentle pressure to the surrounding injured tissues, thereby stopping the postoperative bleeding which was vital to reducing the scar formation. Therefore, the PLGA-PEG-PLGA thermogel could effectively reduce epidural fibrosis, and its efficacy is similar to the CHS gel or improved.

Although we had proved that it was successful to use the thermogel preventing epidural fibrosis in a laminectomy rat model with good biocompatibility and
convenient application, before clinical use of the thermogel, there are still several issues need to be clarified. Firstly, a method assessing the degree of swelling of the thermogel during gelation and how this would affect epidural compression both qualitatively and quantitatively should be adopted in the further study. Moreover, as a novel material aiming to prevent epidural fibrosis, its effects on dural healing and CSF leak need to be further assessed via a dural-tearing model. What’s more, some bone regrowth was noted in our 4-week experimental groups, whether the thermogel will affect the bone formation in a long-term follow-up is still unknown and need to be evaluated in the further study.

**Conclusion**

A thermogel composed of PLGA-PEG-PLGA triblock copolymers was successfully used as a mechanical barrier system to prevent epidural scarring formation in an adult rat model of laminectomy. The biocompatibility of this polymer system was confirmed via *in vitro* tests. *In vivo* application of this thermogel on prevention of epidural fibrosis demonstrated that this thermogel effectively reduced the formation of epidural scarring, and prevented the subsequent adhesion of tissue to the dura mater. Meanwhile, the PLGA-PEG-PLGA thermogel could be very conveniently used during spinal surgery, and no side effects such as infection or foreign body reaction were found.
References:

34. Yu L, Zhang Z, Zhang HA, et al. Biodegradability and biocompatibility of


**Figure legends:**

**Figure 1.** In vitro cytotoxicity of the PLGA-PEG-PLGA triblock copolymer towards NIH-3T3 cells according to various concentrations. Each point represents the mean ± SD (n = 6).

**Figure 2.** Macroscopic observations of the laminectomy site. (A–C) Administering the gel or NS solution. (D–F) Gross anatomical observations of the epidural scar tissues at 1-month post-laminectomy. (D) Membranaceous epidural scar tissues in a PLGA-PEG-PLGA thermogel-treated animal. (E) Funiform epidural scar tissues in a CHS gel-treated animal. These epidural scar tissues could be easily removed in order to re-expose the dura mater (not shown). (F) Dense, thick epidural adhesions covering the dura mater in a control animal.

**Figure 3.** Representative histologic sections with hematoxylin–eosin staining (upper) and Masson staining (lower) under 40x magnification showing different rating of epidural fibrosis. Thermogel group (picture A and D) and CHS group (picture B and E) showed grade 1 according to the aforementioned criteria, while the Control group (picture C and F) showed the grade 3. Comparing with the control group, the extent of adhesion was more slightly in the CHS and thermogel groups and the epidural scar area was also evidently less. Arrows: the dura; asterisks: the scar; SC: the spinal cord.

**Figure 4.** (A) Areas of fibrosis, (B) density of fibroblasts, and (C) density of blood vessel in the groups treated with PLGA-PEG-PLGA thermogel (“Thermogel”), CHS gel (“CHS gel”) or without any barrier materials (“Control”) at 4 weeks postoperation. Significant differences between the control group and the PLGA-PEG-PLGA thermogel/CHS gel groups were noted and specifically marked.
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