

A New Material for Prevention of Epidural Fibrosis After Laminectomy

Oxidized Regenerated Cellulose (Interceed), An Absorbable Barrier

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Abstract: Epidural fibrosis, which may cause persistent back and leg pain, may develop after laminectomy. Several materials have been used in attempts to minimize epidural fibrosis, with varying results. We evaluated the efficacy of an absorbable cellulose adhesion barrier in preventing epidural fibrosis. In 25 New Zealand white rabbits, laminectomies were performed at L3 and L5 vertebrae. The dura mater was covered by the adhesion barrier (Interceed, TC7, Johnson & Johnson, USA) at L3 laminectomy site (group 1), with L5 laminectomy site serving as an internal control (group 2) in each animal. There was no neurological deficit in any of the animals during the postoperative period. Animals were sacrificed at postoperative day 28. The lumbar spine was removed en bloc and placed in neutral, buffered formalin for 72 h. The specimens were then decalcified and embedded in paraffin. Permanent sections of 5 to 7 μ m were stained with hematoxylin and eosin and Masson trichrome dye. Epidural fibrosis was evaluated in a double-blinded manner. The extent of epidural fibrosis was graded as 0, no reaction seen; 1, mild reaction; 2, moderate reaction; 3, extensive reaction, and 4, severe reaction. The histological findings of each group were compared. For the statistical analysis, Wilcoxon signed rank test was used. In group 1, the fibrotic tissue formation was minimal in 19 and moderate in 6 laminectomy sites. In group 2, the fibrotic tissue formation was determined as being extensive in 17 and moderate in 8 laminectomy sites. Statistical analysis showed significant decrease in epidural fibrosis in group 1 ($P < 0.05$). This study showed that Interceed, which is commercially available in the market, especially for abdominal and gynecological surgeries, could be used to prevent epidural fibrosis.

Key Words: epidural fibrosis, adhesion barrier, laminectomy, dura, neurological deficit

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There is a notable agreement in the literature about the rate of complications after surgery of the lumbar spine for herniated intervertebral disc.^{1–3} There are numerous causes for persistent or recurrent symptoms after surgical treatment of herniated lumbar intervertebral discs. Most authors, however, agree that the principal causes of the postoperative radicular syndrome are the recurrence of the disc herniation and excessive epidural scar formation.^{4,5}

The formation of epidural scar tissue is an expected consequence of laminectomy, causing traction on the dura mater or nerve roots or both and resulting in low back or pseudoradicular pain.^{6–8} Cells that generate fibrosis are fibroblasts that come from the adjacent paraspinal musculature.⁷ Epidural scarring is a manifestation of the normal process of wound repair and as such occurs after all surgical interventions on the spine.⁹ This physiological scarring is favored by certain factors such as the fibrous organization of hematomas, keloid reaction, and technical faults in the operation and may become a hypertrophic and enveloping membrane, constituting the so-called postlaminectomy membrane described by LaRocca and Macnab.⁷ This membrane, which was found to result from the destruction of epidural fat, intraspinal hematoma, and advancement of the erector muscles of the spine into spinal canal,⁷ is accepted as being one of the causes of the lumbar pain and sciatic irritation that badly affects the prognosis of some patients after surgery of the lumbar spine. The mechanical tethering of nerve roots, or the dura, by the epidural adhesions may be a contributing factor for a significant subset of patients suffering from persistent back and leg pain after lumbar laminectomy, the so-called failed back syndrome.^{10,11} Another consequence of the presence of epidural scar is that it makes subsequent dissection more time consuming and difficult for the surgeon, with increased risk of complications, such as nerve root injury, dural tears, and iatrogenic instability.^{12,13}

The development of both techniques and materials to prevent the formation and adherence of the tissues to neural elements is, therefore, of importance in improving surgical outcome. Modifications of surgical technique, anti-inflammatory medication, and the use of biologic and synthetic interposing materials, serving as a

mechanical barrier between dura and overlying tissue, have been employed in an attempt to prevent or limit the formation of fibrous tissue. A variety of biological, pharmacological, and synthetic materials have been evaluated to address the issue of scar formation in the posterior spine after laminectomy. Silastic, ADCON-L, Gore-Tex membrane, Dacron, Vicryl mesh, Zenoderm, methacrylate, carboxymethylcellulose, polyethylene oxide, biodegradable polymers, bioelastic polymers, bone grafts, synthetic membranes and foams, free and pedicled fat grafts, sodium hyaluronate, steroids, and anti-inflammatory medications have been utilized with inconsistent results.^{7,8,10,12-30} However, their use in animal models demonstrated moderate success, whereas clinically, their use is yet to be successful. Although fat graft remains the most commonly used material clinically,^{20,31} it has been associated with seroma formation, scar dimpling, limited laminectomy area coverage, and the migration of fat graft, which have been implicated as the causes of several cases of cauda equina syndrome.^{32,33}

Peridural fibrosis has been consistently produced in rabbits, rats, and dogs.^{12,14,17,19-21,25,30} The formation of dense fibrosis at the laminectomy site at least 4 weeks postoperatively in rabbits is a reliable finding and qualifies this animal as an appropriate model for the study of absorbable oxidized regenerated cellulose (Interceed), which has been shown to reduce neural adhesion in a rabbit sciatic nerve model.³⁴

The use of a barrier during surgery to protect raw tissue surfaces as they heal has been shown to be one of the most effective methods of reducing adhesions. Interceed is a product that is used to reduce the likelihood of the development of adhesions. It is a lightweight, tissue-like "fabric" that can be placed at the surgical site. The fabric helps prevent postoperative adhesions by protecting and separating the surfaces in which adhesions are likely to form. The Interceed is laid over the raw areas on completion of surgery and is absorbed over the next 10 to 14 days, during which time the tissues have the opportunity to heal, thus reducing the risk of adhesions. It is mostly used as an adjuvant in open (laparotomy) gynecologic pelvic surgery for reducing the incidence of postoperative pelvic adhesions after the achievement of meticulous hemostasis consistent with microsurgical principles.

This study examines the ability of absorbable oxidized regenerated cellulose (Interceed, TC7, Johnson & Johnson, USA) to inhibit the formation of postlaminectomy epidural fibrosis in rabbits. The effects were examined by quantitative histological analysis.

MATERIALS AND METHODS

Twenty-five male New Zealand rabbits weighing between 3 and 4 kg were utilized for this study after approval was obtained from the University Committee on Animal Resources. To control for surgical technique, the same surgeon performed the surgeries.

Anesthesia was performed with an intravenous injection of ketamine (35 mg/kg) and xylazine (5 mg/kg). The lower half of the back of the rabbits was shaved and a preoperative dose of intramuscular cefazolin sodium (0.1 mg/kg) was administered for infection prophylaxis. The rabbit was positioned prone on the operating table with slight lumbar flexion.

The surgical field was prepared with povidone-iodine (Betadine) soap and solution. The area was draped in an aseptic manner. A posterior midline skin incision was performed from L1 to L5 vertebrae and carried sharply down to the lumbosacral fascia, which was incised sharply to expose the tips of the spinous processes. With blunt dissection, the paraspinal musculature was subperiosteally dissected and the lumbar vertebral segments were exposed. Total laminectomies were performed at L3 and L5 levels in each animal by removing the spinous process with careful bilateral excision of the laminae with the help of a pneumatic burr and fine neurosurgical punches. The laminectomy defects were measured to be approximately 5 × 5 mm. The technique had to be performed meticulously to avoid injury to the spinal cord or the cauda equina. The laminectomy defects were irrigated with sterile saline solution and meticulous hemostasis was obtained. The ligamentum flavum and epidural fat were then removed and the dura mater was exposed. The dura mater was covered by the square of sterilized adhesion barrier (Interceed, TC7, Johnson & Johnson, USA) that was cut to a size of approximately 6 × 6 mm and laid in the L3 laminectomy site (group 1) to be a snug fit and to lie closely to the dura without pressing on it, with L5 laminectomy site serving as an internal control. Thus, each rabbit served as its own control to minimize individual variations in healing. Care was taken to place the material within the laminectomy defect in such a manner that close contact was achieved with the exposed dura. L4 space remained inviolated in each animal, with the paraspinal muscles left intact, thereby providing a soft-tissue barrier to prevent communication of the L3 and L5 laminectomy sites. The wound was closed in layers. A few interrupted 3-0 vicryl sutures were used to reapproximate the lumbosacral fascia, and the rest of the layers were closed in the standard manner. After the recovery period, the animals were evaluated in terms of general medical condition and neurological status and were then allowed cage activity for 4 weeks after surgery.

The animals were sacrificed at postoperative day 28 by a lethal dose of pentobarbital (150 mg/kg). For histological studies, the distal spine (L1-6) was removed en bloc, including the paraspinal musculature, and fixed in neutral, buffered formalin for 72 h. In each specimen, L3 (group 1) and L5 (group 2) laminectomy sites were identified and marked with suture. The L3 and L5 levels were sawed and the entire laminectomy site removed without damage. The specimens were decalcified in 14% neutral ethylenediaminetetraacetic acid for approximately 3 weeks. Completion of decalcification was tested using calcium oxalate. The specimens were then fixed in 10%

buffered formalin, followed by dehydration in ethanol. They were then cleared in xylene, impregnated, and embedded in paraffin. All the decalcification, fixation, and tissue-processing procedures were done at room temperature. Permanent sections of 5 to 7 μm were stained with hematoxylin and eosin. Connective tissue was further evaluated with Masson trichrome stain.

Histological Evaluation

The histological sections (stained with hematoxylin and eosin or Masson trichrome) were evaluated microscopically (Olympus BX-50, Japan) by 2 independent observers (double-blinded manner) for the presence of fibrosis, the density of fibrosis, the vascularity at the fibrosis, the presence or absence of foreign body response, and the extent of normal healing and bone growth. The density of fibrosis was scored as follows: 0, no reaction seen; 1, mild reaction; 2, moderate reaction; 3, extensive reaction, 4, severe reaction.¹³ Additionally, the amount of fibrosis attached to the dura was determined for each section.

Statistical Analysis

Comparison of the scores of the density of fibrosis for the control versus experimental sites was performed using the Wilcoxon signed rank test. *P* value less than 0.05 was considered. Additionally, Cohen κ coefficient was performed for the interobserver's agreement.

RESULTS

There was no neurological deficit in any of the animals and all of them were active, ambulatory, and healthy appearing at the time of sacrifice. The wounds were well healed over all the laminectomy sites without evidence of infection. Three animals died because of anesthetic complications or severe neurological deficit in the early postoperative period associated with the surgical technique learning curve; these 3 were replaced in the study.

In histological analysis, the fibrous tissue could be observed to be present superficially at all the laminectomy sites with no evidence of infection, chronic inflammation, or foreign body reaction at either the implantation or the control sites. The control laminectomy sites revealed abundant fibrotic tissue, densely populated with fibroblasts, with direct apposition to the dura mater by multiple adhesions. The representative histological images for the untreated control specimens are shown in Figure 1. In contrast, the experimental sites consistently exhibited less epidural fibrosis, with the scar tissue appearing less dense and with fewer fibroblasts. This tissue, when present, was often not in direct contact with the underlying dura mater. For the specimens treated with the absorbable barrier adjacent to dura, the overall view is illustrated in Figure 2.

In the experimental group (group 1), the scar formation was minimal (grade 1) in 19 and moderate (grade 2) in 6 laminectomy sites. On the other hand, in control group (group 2), scar formation was determined

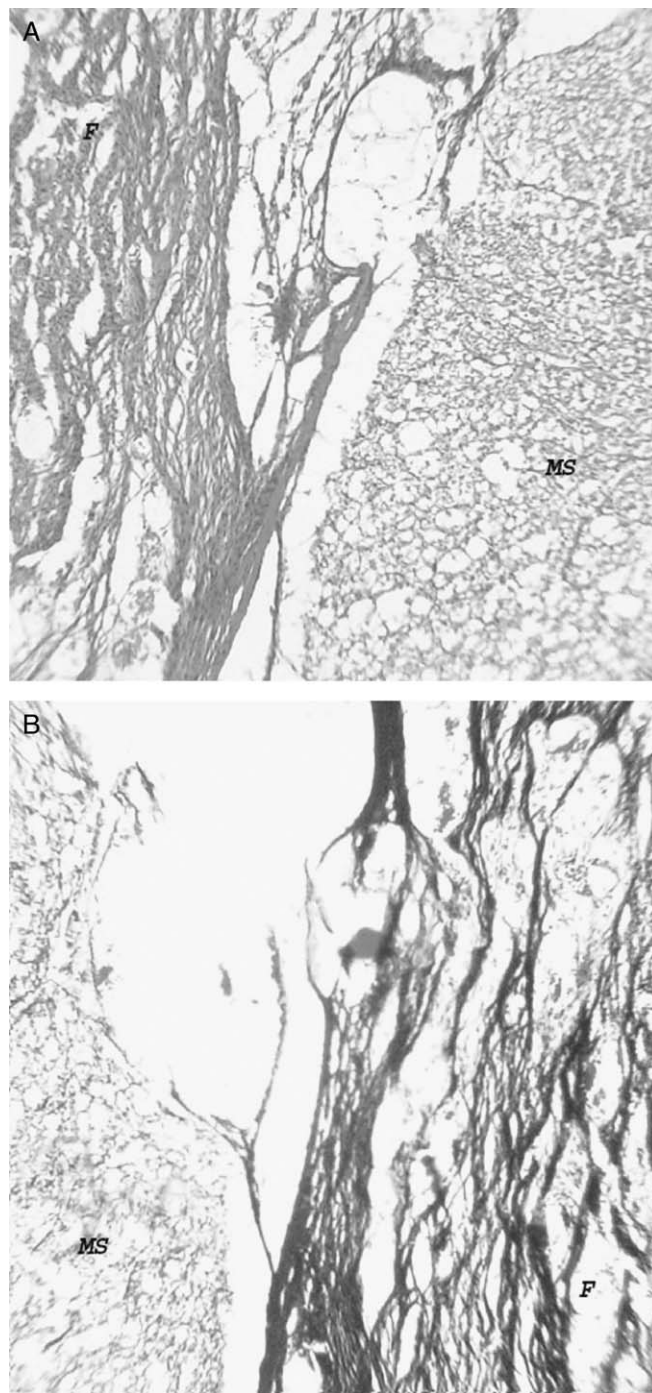


FIGURE 1. The control laminectomy sites revealed abundant fibrotic tissue, densely populated with fibroblasts, with direct apposition to the dura mater by multiple adhesions. MS, medulla spinalis; F, fibrous tissue. A, hematoxylin and eosin, $\times 10$ and B, Masson trichrome, $\times 10$.

to be extensive (grade 3) in 17 and moderate (grade 2) in 8 laminectomy sites.

Compared to the control sites, Interceed absorbable barrier significantly reduced the formation of epidural

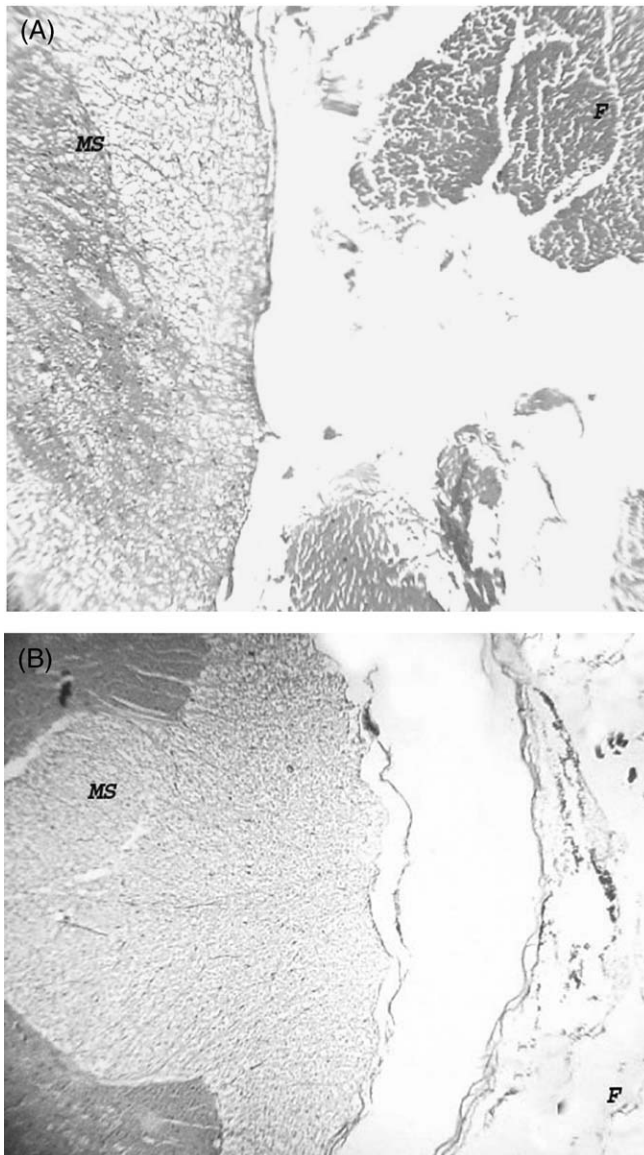


FIGURE 2. The section of a laminectomy site treated with absorbable oxidized regenerated cellulose showing less epidural fibrosis, with the scar tissue appearing less dense and with fewer fibroblasts. MS, medulla spinalis; F, fibrous tissue. A, hematoxylin and eosin, $\times 10$ and B, Masson trichrome, $\times 4$.

fibrosis and its area of contact with the dura mater (Tables 1 and 2). Additionally, interobserver agreement was found to be perfectly concordant (Cohen κ coefficient: 1000).

DISCUSSION

Epidural fibrosis occurs when there is a deposition of fibrous tissue in the epidural space surrounding the nerve root. This process is often initiated by injury or trauma to the epidural space related either to epidural exploration³⁵ or to surgical procedures involving the

TABLE 1. Definition of Criteria Employed for Scoring for Histological Analysis (14)

| | |
|---------------------|---|
| Grade 0 (none) | Absence of fibrosis |
| Grade 1 (minimal) | Fibrosis not adherent to the dural sac or nerve roots, less than 25% involvement |
| Grade 2 (moderate) | Fibrosis adherent to the dural sac or nerve roots, less than 50% involvement |
| Grade 3 (extensive) | Fibrosis adherent to the dural sac and nerve roots, less than 75% involvement |
| Grade 4 (severe) | Fibrosis throughout the vertebral canal, encompassing the dural sac and nerve roots, up to 100% involvement |

disc.³⁶ Fibrosis often produces adhesions tethering the nerve root to adjacent tissues. The tethering may then impede nerve mobility and increase tension on the nerve during motion, leading to nerve injury.

Postlaminectomy epidural fibrosis after laminectomy significantly increases the hazards of revision spine surgery and may contribute to the occurrence of failed back syndrome.^{11,37} Attempts to limit the formation of this tissue through variations in surgical technique,²¹ microdiscectomy,³⁸ the use of anti-inflammatory medications,^{17,26} and several biologic and synthetic materials, including free fat graft,^{7,8,15,18,20,39,40} Gelfoam and Avitene,^{17,41} Silastic,⁸ polylactic acid,⁴² and Gore-Tex membranes,⁴³ have generally been unsuccessful.^{10,39,44} The rationale for their use was to limit the direct connection between the dense fibrotic tissue, originating from the fibrous layer of the periosteum and within the deep surface of the paravertebral musculature, from extending into the neural canal and adhering to the dura and nerve roots. At present, the use of free fat graft, although associated with numerous drawbacks including seroma formation, dimpling of the scar, limited supply, and multiple case reports of cauda equina syndrome,^{32,33} remains the gold standard, and many surgeons will empirically cover the exposed dura with subcutaneous fat after a laminectomy. The fat does not prevent the formation of scar, but it reduces the adhesions and maintains a good anatomical plane between dura and surrounding tissue.^{15,18,19,24,40}

There are several potential origins for fibroblasts, which cause the postlaminectomy epidural fibrosis,

TABLE 2. Statistical Significance Between the Control (Distal) and Experiment Groups (Proximal)

| Group | Observer 1 | | Observer 2 | |
|--------------------|------------|--------|------------|--------|
| | Proximal | Distal | Proximal | Distal |
| n | 25 | 25 | 25 | 25 |
| Mean | 1.24 | 2.68 | 1.2400 | 2.68 |
| Std. Deviation | 0.436 | 0.476 | 0.436 | 0.476 |
| Std. Error of Mean | 0.87 | 0.95 | 0.87 | 0.95 |
| Minimum | 1.00 | 2.00 | 1.00 | 2.00 |
| Maximum | 2.00 | 3.00 | 2.00 | 3.00 |
| P value | P < 0.001 | | P < 0.001 | |

P value. Wilcoxon Signed rank test.

seen in humans. They may arise from the paraspinous musculature, ligamentum flavum, posterior longitudinal ligament, or the annulus fibrosus.⁷ They may also migrate from areas distant from the laminectomy site. Chemoattractant factors or migration-stimulating factors released by the lysis of red blood cells may result in the influx of these scar-forming cells or their precursors.²⁸ So meticulous hemostasis at the operative site is essential.

In the current study, we tested the hypothesis that the use of absorbable oxidized regenerated cellulose barrier will be safe, significantly reduce the extent of epidural fibrosis after laminectomy, and prevent the consequent adhesion of this tissue to the dura mater. For this purpose, a bilateral lumbar laminectomy rabbit model was employed, with the efficacy of the barrier assessed using qualitative and quantitative histological methods. Canine and rabbit models of epidural fibrosis after laminectomy have been utilized extensively.^{7,12,14,17,19–22,25,27,30} The rabbit is a more difficult experimental animal because of its small size and fragility, particularly in regard to anesthesia. Spinal cord injury occurs easily with minor trauma during laminectomy because the rabbit has a small epidural space, with conus medullaris extending approximately to the L5 segment. The low cost and homogeneity among animals of the same size, however, make the rabbit an attractive subject for these kinds of studies.²⁸ Some reports in the literature^{19,20} agree that significant bone regeneration will be seen about 9 weeks postoperatively in rabbit models. This report limited the evaluation period of fibrosis to only 4 weeks to eliminate the confounding variable of bone growth.

Oxidized regenerated cellulose (Interceed) is a barrier that adheres to the site of injury, gelatinizes, and purportedly keeps the opposing tissue layers separated during the healing process. The Interceed was approved by the Food and Drug Administration (FDA) in 1989 as the first product specifically indicated for reduction of postsurgical adhesions, especially in pelvic and abdominal surgeries. Many studies have since then shown that the proper use of Interceed is useful in reducing the formation of adhesions after abdominal and pelvic surgeries.^{45–47} It has been recently reported that Interceed influences the expression of factors commonly accepted to be associated with adhesiogenesis, especially tending to decrease the expression of transforming growth factor- β 1 in adhesion fibroblasts.⁴⁸

Although the result of this study has a limitation of small sample size, it showed absorbable oxidized regenerated cellulose barrier to be safe and well tolerated in the rabbit model and to significantly reduce both the formation and direct contact of the fibrotic tissue with the underlying dura. In all the implantation sites evaluated, the soft tissues appeared to be well healed at the time of sacrifice, with microscopic evaluation of tissue showing no evidence of infection, chronic inflammation, or foreign body reaction.

In conclusion, the prevention of epidural fibrosis after laminectomy represents a major challenge in spine

surgery. The present study suggests that absorbable oxidized regenerated cellulose merits further evaluation as a potential treatment to inhibit the formation of epidural scar after laminectomy. Rigorous and extensive controlled trials should be undertaken on groups of patients undergoing lumbar surgery with or without the mentioned barrier. Such trials may help determine the ultimate value of this barrier.

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