

# Shape memory hydrogels –A novel material for treating age-related degenerative conditions of the Spine

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## Abstract

Hydrogels are water insoluble **hydrophilic polymers** used in a wide range of medical products such as, drug delivery, tissue replacement, heart surgery, gynecology, ophthalmology, plastic surgery, and orthopedic surgery<sup>1,2,3,4</sup>. These polymers exhibit **low toxicity**, reduced tissue adherence, and are **highly biocompatible**. A class of hydrogels, hydrolyzed polyacrylonitriles (**HPAN**), possess unique shape memory properties which when combined with biocompatibility, **mechanical strength** and **viscoelasticity** make them ideal for treating certain degenerative conditions of the spine. Animal and other *in vitro* studies show that the hydrogel was biocompatible and well-tolerated by host tissues. This paper focuses on two specific indications in spine surgery which demonstrate the potential of hydrogel-based technology to provide significant treatment advantages.

## Introduction

Hydrogels are able to absorb large quantities of water relative to their initial weight because of their intrinsic hydrophilicity. As a result of this propensity to imbibe large quantities of water, the material can be implanted into the body in a collapsed, low volume dehydrated state and then expanded *in vivo* through absorption of body fluids to assume a different shape comprising a much greater volume. Since the composition by mass of the expanded polymer is principally water and/or body derived fluids, the swollen object is highly biocompatible producing minimal inflammation following implantation.

Although many different hydrogels have been developed based on various chemistries, **hydrolyzed polyacrylonitrile (HPAN)**, has been extensively studied and used in the formulation of **contact lenses**, drug delivery, gynecological, and orthopedic implants. This group of thermoplastic hydrogels is based on acrylic multiblock copolymers. A heterogenous reaction of the

hydrophobic base polymer polyacrylonitrile with sodium hydroxide produces a water soluble block copolymer which upon phase separation yields crystalline clusters of hydrophobic nitrile functional groups and amorphous hydrophilic water binding domains. The hydrogel is produced through a simple chemical reaction using **no monomers, cross-linkers, catalysts, or other toxic residuals**<sup>5</sup>.

Advantageous properties of the HPAN block copolymer include **biocompatibility and biocompatibility**. HPAN also exhibits similar elasticity and tensile strength compared to tissues such as vitreous body, cartilage and the nucleus pulposus of the intervertebral disc.. The hydrogel's elasticity can also be controlled by adjusting the chemistry and the water content allowing the material to be used in various applications such as replacement of the aforementioned tissues.

The shape memory property of the hydrogel is a unique attribute which provides treatment options in situations where insertion dimensions are critical. These properties are particularly well suited to indications in minimally invasive spine surgery wherein the collapsed, minimized, insertion form of the hydrogel configured to a particular shape, transforms into a larger and different, functional shape upon implantation. In this instance, the minimized shape facilitates insertion with little tissue damage and the fully hydrated state allows the implant to function as either a nucleus augmentation implant or an interspinous spacer (Figure 1).



**Figure 1: Shape memory, *in vivo* expanding hydrogel implants in a nucleus augmentation (top) and interspinous spacer (bottom) application.**

Prior to clinical introduction, hydrogel implants were subjected to an extensive battery of *in vitro* and *in vivo* animal tests to evaluate the safety and functional properties of the material. The *in vitro* and animal tests include but are not limited to acute and chronic toxicity, genotoxicity, systemic toxicity, irritation, and Intramuscular Implantation testing. All testing was conducted using Good Laboratory Practices (GLP) at an accredited independent laboratory.

#### **Large Animal Safety Study**

A large animal study was performed to evaluate the biologic response to the spinal nucleus implant following insertion into the disc space of runt cows. The histopathologic response to the implant was compared to normal disc tissue following a comparable surgical procedure without implant insertion. Gross neurologic exams and histological observations were performed to demonstrate lack of injury to the spinal cord and surrounding tissues. Additionally, **implant safety** was further investigated through major organ **histology**, **hematology and blood serum chemistry** evaluations.

#### **Materials and Methods**

Seven “runt” cows (K-Bar strain) were utilized to evaluate the nucleus replacement device. Three test devices were

placed in the lumbar spine of each animal. The implantation procedure involved a lateral approach to the spine to expose the disc spaces between T8 and S1 devices were placed at L1-L2, L3-L4, and L4-L5. L2-L3 served as a surgical control undergoing identical surgical procedures without device insertion.

Evaluation times were 12 weeks (3 animals), 24 weeks (3 animals) and 52 weeks (1 animal). All animals were subjected to a comprehensive necropsy consisting of examination of the external surface of the body and the cranial, thoracic, and abdominal cavities, and their contents. Tissue specimens were collected from major organs and regional lymph nodes (axillary, iliac, mesenteric). The spine and spinal cord were removed *in toto* from T12-L6 in preparation for histological analysis.

#### **Results**

##### 12, 24, 52 Weeks

##### **Necropsy**

The animals were observed as clinically normal for the duration of the study following surgery. Physical examinations yielded no remarkable observations and neurologic exams for all animals were normal with no abnormal findings in relationship to peripheral nerves of the spinal cord. No remarkable findings were noted at necropsy.

##### **Hematology and Blood Serum Chemistry**

There were no remarkable observations or changes in body weight values. Additionally, there were no remarkable changes observed in the hematology and serum chemistry profiles. All parameters were within acceptable ranges.

##### **Histology through the Intervertebral Disc – Figure 2**

The hydrogel devices were encapsulated with an inner fibrovascular granulation tissue layer containing minimal to mild numbers of inflammatory cells (macrophages, neutrophils, and lymphocytes), and an outer collagen-dense fibrous and fibrocartilage layer. The devices were well tolerated by the host. The amount of inflammation in association with the granulation tissue surrounding the device was expected. The inflammation was minimal, localized, and did not appear to cause any additional notable or secondary changes. In contrast to Controls, the surface of the granulation tissue and fibrocartilage in contact with the space or device surface was flat, suggesting that the intradiscal device provided for some internal pressure to the disc space.

### *Spinal Cord and Nervous Tissue* **Histopathology**

Spinal cord and nervous tissue histopathology included evaluation of the loose epidural tissue and vessels (if present), dura mater, subepidural space, arachnoid membrane, subarachnoid space, pia mater, spinal artery and vein, white columns, central canal, gray horns and nerve cells, nerve roots and ganglia (if present). Components of the spinal cords evaluated did not show any remarkable changes.

### **Conclusion**

In this study, the host tissues, either intervertebral or spinal, did not react adversely to the presence of the device material. The device material was well tolerated by the host tissues. The changes that were observed were expected, incidental or associated with the experimental surgical manipulations and the surgical techniques required to maintain the device in the intravertebral disc space.

### **Neurobiocompatibility Study**

In another animal study, **neurotoxicity** testing of a particulate form of the hydrogel introduced into a rabbit intra-discal implant model was conducted.

The purpose of the study was to determine the biocompatibility/neurobiocompatibility of HPAN hydrogel particulate (as investigated in 2 size ranges). The study included a worse case scenario for wear debris; particulate equivalent in two size ranges (< 10 micron and 10-300 micron) was injected into both the epidural and intradiscal space in a rabbit model.

This allowed the evaluation of the subchronic biocompatibility of the polymer particles in the nervous tissue (dura mater and nerve roots), as well as within the intradiscal space. The biocompatibility of the hydrogel particulate was investigated in two size ranges when implanted in two locations. In addition, any effect of the particulate on blood serum chemistry and hematology was assessed.

### **Methods**

Twenty animals were utilized in the study. The study consisted of four treatment groups of male New Zealand white rabbits. Group 1 animals were treated with saline, Group 2 animals received small particle hydrogel, and Group 3 animals received large particle hydrogel. Group 4 animals functioned as a sham control group; delivery catheters and needles were placed within the treatment sites, but no test article was administered to these animals.

Each animal received hydrogel particulate at 2 levels in the spine; one in the lower thoracic region at approximately T10 and one in the lumbar region at approximately L3. At each level, the animal received two injections- one into the intradiscal space and one adjacent into the spinal canal at the same level. The quantity of particulate in these two injections together modeled the break-up or particulation of one-half of the implant, where part of the particulate remains in the disc space and part has migrated into the spinal canal. The hydrogel particulate was mixed with saline prior to injection to form a slurry.

On Day 1, each animal underwent a surgical procedure wherein the epidural spaces at the levels of T9 and L4 and the intradiscal spaces at the levels of T10/T11 and L2/L3 were exposed. Test article (HPAN 90 Hydrogel Particulate) or vehicle control (saline) was then injected into both the epidural and intradiscal spaces.

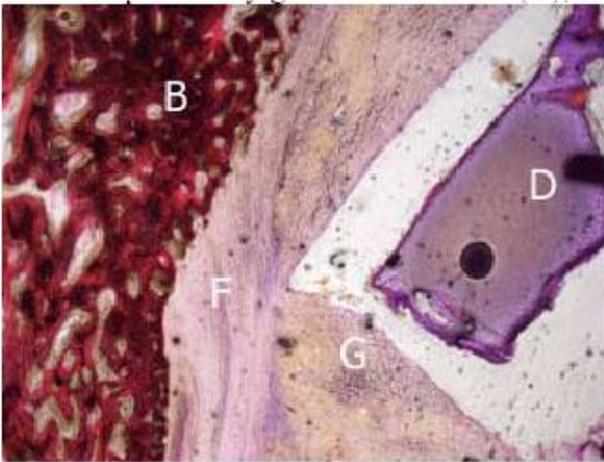
### **Results**

No remarkable clinical observations or changes in body weight values were attributed to the presence of test material. In addition, all animals were assessed as clinically normal by physical examination prior to their necropsy with only a few incidental findings. There were no remarkable changes observed in the hematology and serum chemistry profiles at 30 and 90 days. Additionally, there were no appreciable differences between treatment groups or time points based on these values. Histologically, the implant particles identified in the tissues evaluated for Groups 2 and 3 after 30 days showed that, regardless of tissue location or particle size, the hydrogel particles elicited minimal to mild inflammatory changes, with macrophages and giant cells phagocytizing some particles and/or aggregating around the particles. After 90 days, the implant particles identified in the tissues evaluated for Groups 2 and 3 showed that, regardless of tissue location or particle size, the hydrogel particles elicited minimal inflammatory changes, with macrophages and giant cells phagocytizing some particles and/or aggregating around the particles.

The particles and inflammation remained within the epidural space, its vessels, the adipose and loose connective tissue, and on the dura mater's surface. These were never seen beneath the dura mater (in the pia-arachnoid space) or within the nervous tissues. Also, the nervous tissue components of the spinal cords evaluated did not show any notable changes.

## Conclusion

After 30 and 90 days, based on the clinical pathology parameters, the presence of implant material did not cause any notable systemic changes. In addition, the histological changes observed in the tissues evaluated with implant material were considered to be minimal to mild. Therefore, the implant material, regardless of size, appeared to be safe with minimal host tissue reaction. The implant particles appeared to be contained by the host's inflammatory cells (macrophages and giant cells). Distribution of particles to regional lymph nodes was not evident.



**Figure 2: Animal No. 1105, intervertebral disc space (L4/L5) containing hydrogel device (D) that was encapsulated with granulation tissue (G), fibrous tissue (F), and bone (B), (15x).**

## Unique Hydrogel solution for degenerative disc disease: Case Series

Degenerative disc disease (DDD) is among the most common spinal pathologies impacting up to 10-15% of adults. Both biochemical and biomechanical factors contribute to the development of DDD. The degeneration is associated with diminished water-binding capabilities of the nucleus pulposus leading to disc dehydration, volume reduction, changes in cellular activity, biomechanical changes and painful symptoms<sup>6</sup>. Patients are initially treated with non-surgical pain management techniques such as anti-inflammatory medications and physical therapy, but these therapies often provide only temporary relief. When non-surgical intervention fails, patients are often recommended for fusion or total disc arthroplasty both highly invasive

surgeries with significant associated morbidity. Clearly, a meaningful solution for the treatment gap existing between conservative care and invasive surgical intervention is needed.

The **GelStix™** Nucleus Augmentation Implant provides a ground-breaking approach for treating lower back pain associated with degenerative disc disease and aging. The GelStix™ implant composed of RMI's proprietary polymer is shaped in the form of an elongated hydrogel matchstick which can be inserted under local anesthesia through the same 18 gage needle used to perform a diagnostic discogram or for administration of intradiscal medicine – thus sparing the patient a secondary intervention. The GelStix™ Nucleus Augmentation hydrates through the absorption of the body's own fluids and expands nearly ten times in volume (with minimal increase in length) in less than 15 minutes. **A single treatment brings nearly 1 cc of hydrogel to the disc. Similar to the native nucleus, the implant acts as a reservoir of permanent hydration producing increased pressure, improved fluid exchange and pH balance thus restoring the disc to a healthy state<sup>7</sup>.**

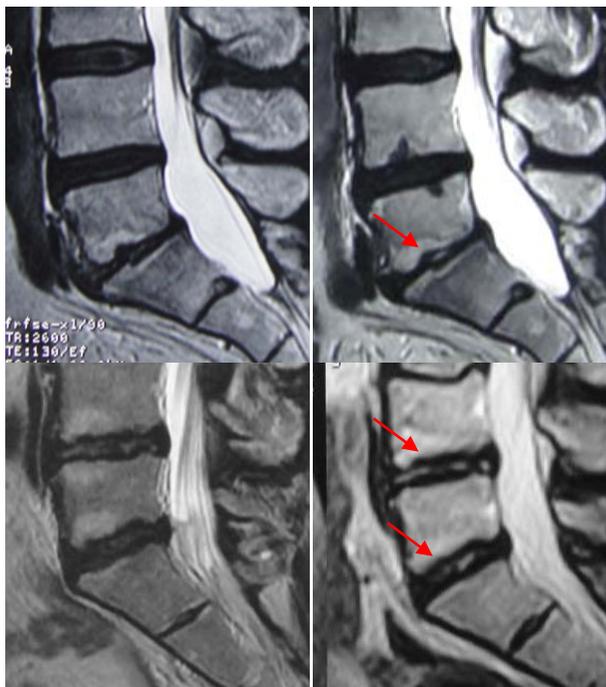
A twenty patient post-market clinical study was initiated to evaluate the potential for GelStix to reduce backpain in a subset of patients diagnosed with degenerative disc disease. The primary inclusion criteria was discogenic pain with minimal radicular pain confirmed by radiographic imaging and discography. To date, ten patients have been treated with GelStix (eight that have reached followup timepoints) for moderate to severe discogenic back pain in most cases persisting for at least 1 year with unsatisfactory results from conservative care (Table 1). In addition to back pain, four patients (50%) experienced mild to moderate radicular pain and one patient had Grade 1 spondylolisthesis. Two patients had prior discectomies at the affected level.

All procedures were performed using local anesthesia. The needle was introduced into the nucleus through a posterolateral approach under fluoroscopic guidance. Provocative discography was performed to confirm diagnosis. Hydrogel implants were loaded into the needle using pre-assembled sterile cartridges. Two or three implants were delivered into each disc level.

**Table 1: Patient Data - GelStix™ post-market study.**

	BCN01	BCN02	BCN03	BCN04	BCN05	BCN06	BCN07	BCN08
<b>Sex</b>	Male	Female	Female	Male	Female	Male	Male	Female
<b>Age</b>	65	48	45	48	57	38	66	51
<b>Previous Surgery</b>	Left endoscopic discectomy L5-S1 in 2005		L5-S1 micro discectomy in 2001					
<b>Diagnosis</b>	DDD at L5-S1	DDD at L4-L5 and L5-S1	DDD at L5-S1	L4-L5 Spondy Grade I	DDD at L4-L5	DDD at L5-S1	DDD at L5-S1	DDD at L4-L5
<b>Lower Back Pain</b>	For 2 Mo	For 1 Yr	For 1 Yr	For 2 Yr	For 2 Yr	For 3 Yr	Yes	Yes
<b>Leg Pain</b>	None	None	Right leg radiating	Right leg radiating	Left leg radiating	Right leg radiating	None	None

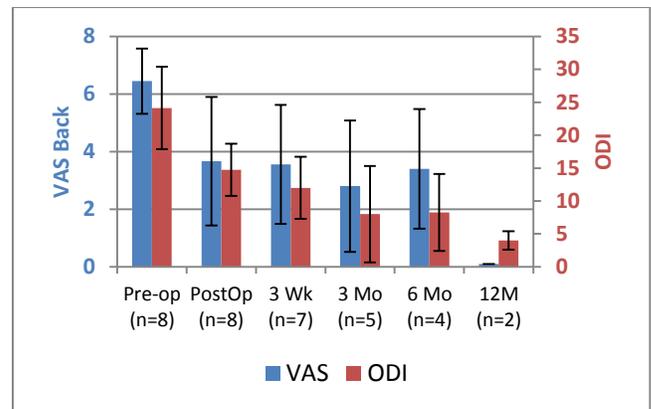
The primary outcome measurement of the study was radiographic evaluation and pain scores, Oswestry Disability Index (ODI) or Visual Analog Scale (VAS).



**Figure 3: Preoperative and three week T2 weighted MRIs of patient BCN01 (top) with GelStix™ at L5/S1 and BCN02 (bottom) with GelStix™ implantation at L4/L5 and L5/S1.**

As of the date of this writing, six patients (75%) showed a significant decrease in back pain quantified with ODI and/or VAS at all timepoints evaluated. Four of the eight patients are more than six months post-procedure and continue to show significant reduction in back pain as

evidenced by improvement in Oswestry and VAS back pain scores. The exception was patient BCN03, who was diagnosed with Grade 1 spondylolisthesis in conjunction with degenerative disc disease. Somewhat unexpectedly, three of the four patients with leg pain had complete leg pain relief following treatment.



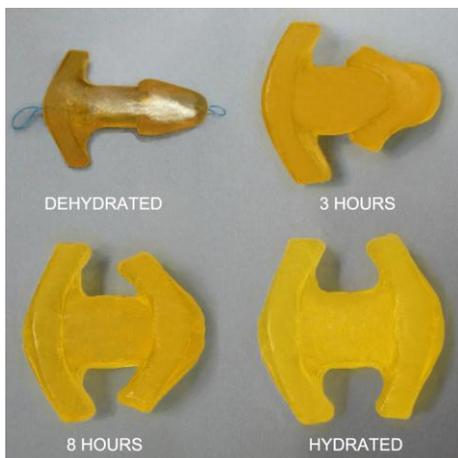
**Figure 4: Back Visual Analog Scale and Oswestry Disability Index following GelStix™**

These initial cases show that GelStix™ is a safe treatment with no reported complication or adverse events when used as indicated. Patient follow-up results show dramatic reduction in pain at all timepoints evaluated. These early data suggest that GelStix holds significant promise for treating early stage degenerative disc disease in a cost effective, non-invasive manner. Additional cases will be performed to refine the scope of the indication and treatment limitations.

#### Hydrogel Treatment for Stenosis

Interspinous spacers are an attractive alternative to fusion for the treatment of lumbar spinal stenosis (LSS), a common degenerative condition that causes a narrowing of the canal and neural foramen. Stenosis leads to the painful condition, neurogenic intermittent claudication (NIC) and is the most common cause of serious back pain in adults  $\geq 60$  years of age<sup>8</sup>. During extension of the spine, painful symptoms worsen because of increased neurologic compression. On the contrary, flexion in the spine relieves these symptoms. An interspinous spacer distracts (flexes) the two adjacent spinous processes at the afflicted level and prevents the pathological extension.

Treatments for spinal stenosis vary from non-surgical pain management to serious surgical intervention. Decompression laminectomies and fusions are the most common surgical solutions to LSS, but both involve inherent risks<sup>9,10</sup>. Over the course of the past 5-10 years, interspinous spacers have grown in popularity as a less invasive alternative<sup>11</sup> to treating spinal stenosis. More recently however, enthusiasm has waned due to the high associated complication rate (up to 28.9%) due to spinous process fracture observed with titanium and polyetheretherketone (PEEK) implants<sup>12</sup>. Hydrogel provides an attractive material for this application because of its elastic response to loading and its ability to conform to the bony anatomy of the interspinous space. The viscoelastic HPAN hydrogel, GelFix™ allows normal motion while selectively restricting painful extension. GelFix™ provides a soft distraction, in contrast with more rigid conventional materials such as titanium and PEEK.

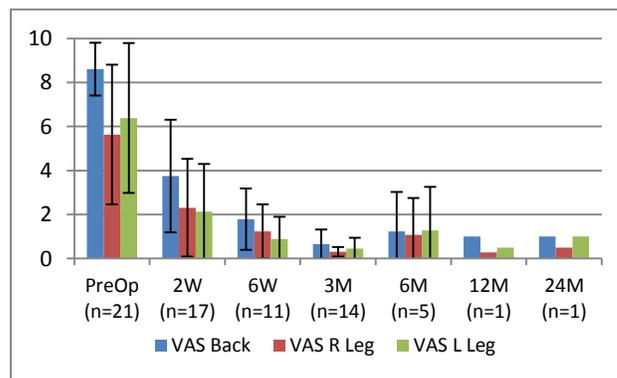


**Figure 5: GelFix™ is implanted dehydrated and expands with body fluid in vivo.**

Approximately 400 GelFix™ procedures have been performed to date. In 2009, a twenty-five patient clinical outcomes study was initiated to assess the ability of

GelFix™ to reduce back and leg pain associated with spinal stenosis. The primary inclusion criterion for this study was painful stenosis relieved by flexion, but patients with discogenic pain were also included. The twenty-one patients treated thus far show a dramatic and prolonged decrease in both leg and back pain on the Visual Analog Scale (**Figure 6**) and Oswestry Disability Index (**Figure 7**). There have been no complications or adverse events associated with the GelFix™ treatment to date.

The longest term follow-up is two years and pain score measurements showed significant drops in both VAS Leg (89%) and ODI (55%) at this point in time. The average improvement in Zurich Claudication Questionnaire (ZCQ) scores for symptom severity and physical function at 6 months were 43.8% and 35.7% respectively. The 80% ZCQ patient satisfaction with an average raw score of 1.46 demonstrates a high treatment success rate at 6 months. It is important to note that although the product is not specifically indicated for the treatment of back pain, nearly every patient experienced a reduction in back pain measurements at all time points. This suggests that the indication for the product may ultimately be expanded to include some level of back pain as well as leg pain due to stenosis. These findings will be substantiated in a larger scale clinical outcomes study currently underway.



**Figure 6: Visual Analog Scale (VAS) from GelFix™ clinical study.**

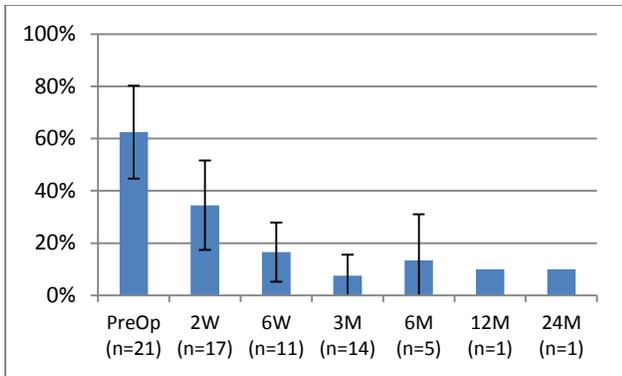


Figure 7: Oswestry Disability Index (ODI) from GelFix™ clinical study.

T2 weighted MRIs (Figure 8) demonstrate posterior height increase and a resulting increase in the central canal. Other cases included GelFix™ adjacent to a fused level. Another patient had previous surgery where three levels of dynamic facet augmentation screws were implanted (S1 to L3). The patient developed degenerative pain at L2/3. GelFix™ was implanted at that level (Figure 9), and it led to a dramatic decrease in pain at 6 months: 97% VAS back, 87% VAS right leg, 87% VAS left leg and a 89% ODI reduction.

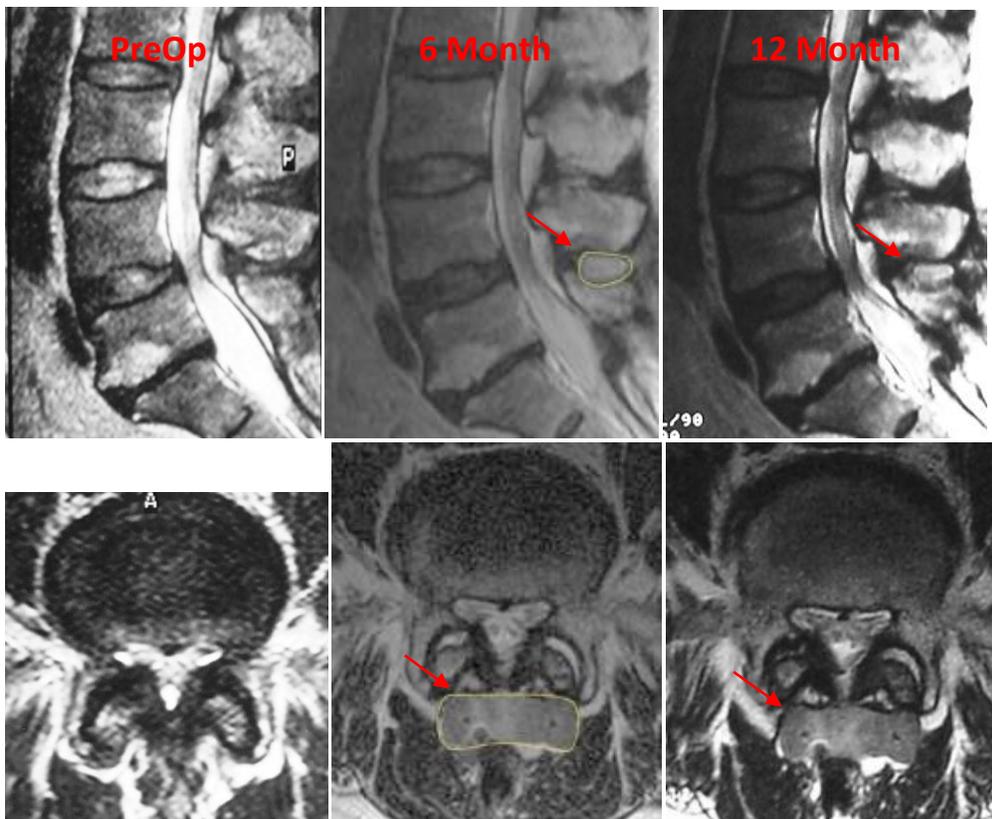
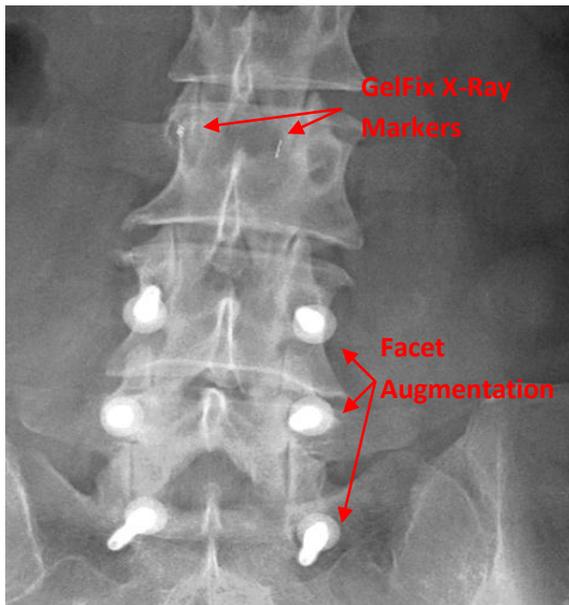


Figure 8: Sagittal and axial T2 weighted MRI at PreOp, 6 months (implant outlined in yellow) and 12 months.

**Table 2: Zurich Claudication Questionnaire Scores for Symptom Severity, Physical Function, and Patient Satisfaction**

Follow-up	Symptom Severity	Physical Function	Patient Satisfaction	Number of Patients
PreOp	3.8 ± 0.7	2.9 ± 0.6	-	19
2 Week	2.4 ± 0.7	2.0 ± 0.5	87.5% (1.6 ± 0.6)	12
6 Week	2.0 ± 0.7	1.6 ± 0.5	100% (1.4 ± 0.5)	10
3 Month	1.6 ± 0.6	1.2 ± 0.3	100% (1.1 ± 0.3)	14
6 Month	1.7 ± 1.2	1.4 ± 0.8	80% (1.5 ± 0.7)	4



**Figure 9: 3 weeks post operative Gelfix™ implantation at L2/3 with previous facet augmentation surgery.**

### Conclusion

Hydrogel implants provide attractive alternatives to traditional materials such as PEEK and metal in treating degenerative conditions of the spine. Animal studies demonstrate that the HPAN hydrogel implants are safe and biocompatible with only a minimal amount of inflammation associated with long term (up to one year) implantation. Capitalizing on the shape memory properties to facilitate minimally invasive surgery, implants based upon hydrogel have been developed to treat spinal stenosis and low back pain associated with degenerative disc disease. Early findings from human clinical data are promising and suggest that hydrogel implants will one day figure prominently in the

continuum of care between conservative, non-operative treatment and major surgery

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