Can Prevention of a Reherniation Be Investigated?

Establishment of a Herniation Model and Experiments With an Anular Closure Device

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Study Design. Biomechanical in vitro study.

Objective. To establish a reliable in vitro herniation model with human cadaver spines that enables evaluation of anular closure devices.

Summary of Background Data. Biomechanically, it is desirable to close anulus defects after disc herniation to preserve as much nucleus as possible. Multiple anular closure options exist to prevent reherniation. A reliable test procedure is needed to evaluate the efficacy and reliability of these implants.

Methods. Two groups of human lumbar segments (n = 6 per group) were tested under cyclic loading until herniation occurred or 100,000 load cycles were applied. One group contained moderate/severe degenerated discs. A second group had mild degenerated discs. Intradiscal pressure was measured in the intact state to confirm disc quality.

If herniation occurred, the extruded material was reinserted into the disc and the anulus defect was treated with the Barricaid anular closure device (Intrinsic Therapeutics, Inc., Woburn, MA). Disc height and 3-dimensional flexibility of the specimens in the intact, defect, and implanted states were measured under pure moments in each principal motion plane. Afterwards, provocation of reherniation was attempted with additional 100,000 load cycles.

Results. Likelihood of herniation was strongly linked to disc degeneration and supported by the magnitude of intradiscal pressure. In moderate/severe degenerated discs, only 1 herniation was created. In mild degenerated discs, herniations were reliably created in all specimens. Using this worst-case model, herniation caused a significant reduction of disc height, which was nearly restored with the implant. In no case was reherniation or implant migration visible after 100,000 load cycles after Barricaid implantation.

Conclusion. We established a human herniation model that reliably produced nucleus extrusion during cyclic loading by selecting specimens with low disc degeneration. The Barricaid seems to prevent nucleus from reherniating. The reliability of this method suggests the opportunity to investigate other anulus closure devices and nucleus replacement techniques critically.

Key words: in vitro test, disc herniation provocation, biomechanics, annulus sealing, spinal motion segments.

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T he surgical standard for the treatment of herniated or ruptured intervertebral discs is to decompress the nerves by removing the sequestrated material, followed by a partial or complete nucleus removal to avoid a reherniation. Removing too much nucleus material can lead to non-physiological biomechanical behavior of the treated segment, whereas removing too little material can increase the reherniation risk.1,2 Nucleus removal causes increased flexibility and a loss in disc height.3,4 This could overload the facet joints, further narrow the intervertebral foramina, and compress the nerve root.5,6 After a longer period, degeneration of the anulus may occur due to the resulting compressive loading of the anular ring,7–9 and larger disc bulging.10 Symptomatic reherniation after lumbar discectomy ranges from 3% to 27%.11 Extrusion from the disc has also been reported for nucleus replacement implants.4

It would be desirable to close the anulus defect to preserve as much nucleus material as possible. The risk of reherniation of disc material may be reduced through the use of implants, but only a few such devices have been developed, and most have failed.2,12–14 Prior devices in clinical use demonstrated a decrease in recurrent herniations, but some device extrusions were observed as no bone anchoring was provided. Therefore, Intrinsic Therapeutics, Inc. (Woburn, MA) developed a next-generation anular closure implant, the Barricaid, which is anchored to the adjacent vertebral body to ensure device stability independent of anular integrity.
Functional spinal units from calf spines have been used to investigate the extrusion risk of implants which replace the nucleus, and initial attempts using this model have also been undertaken to test annulus closure strategies. However, if the size of an implant does not fit the geometry of the calf spines, such tests have to be performed using human specimens.

A few biomechanical studies have shown that it is not easy to produce a reliable disc herniation in human specimens. Only very high loads with complex bending produced a prolapse in about a third of the tested specimens. Both studies showed that, in most cases, it is the bony structures, such as the endplate or vertebrae that failed. These studies also showed that slightly degenerated lumbar discs from subjects between 40 and 50 are most susceptible to prolapse, which is consistent with clinical findings and which could be explained and confirmed with a finite element study.

The aim of this study was to establish a reliable in vitro herniation model with human specimens according to the degree of disc degeneration. We hypothesized that the likelihood of a herniation risk is dependent on the degree of disc degeneration. Furthermore, a new annulus closure implant was tested under cyclic loading conditions.

**MATERIALS AND METHODS**

**Test Procedure**

Twelve human L2–L3 and L4–L5 functional spinal units were used in this experiment (Table 1). Before testing, radiographs were obtained (Faxitron 43805, Hewlett Packard, Palo Alto, CA).

As we hypothesized that the disposition for a herniation is dependent on the degree of disc degeneration, these specimens were assigned to 2 groups of 6 segments with different degrees of degeneration. One group had moderate/severe degenerated discs (grade 2 and grade 3) and the other group had mild degenerated discs (grade 1). The degree of disc degeneration was evaluated from the radiographical images using a standardized grading system, which covers the 3 main radiographical signs of disc degeneration: “height loss,” “osteophyte formation,” and “diffuse sclerosis.” On lateral and anteroposterior radiographs, each of these 3 variables was graded individually on a scale from 0 to 3. Based on the sum of these 3 scores, an “overall degree of degeneration” was assigned to each disc on a 4-point scale from 0 (no degeneration) to 3 (severe degeneration). The quality of the disc was further confirmed by intradiscal pressure (IDP) measurements in the intact state of the specimens. An IDP sensor (MIPM GmbH, Mammendorf, Germany) was inserted into the center of the disc to obtain the pressure of the nucleus. If the disc is free of degeneration, the nucleus mainly features hydrostatic properties and thus even distribution of IDP across the nucleus tissue. Disc degeneration would change the IDP profile and therefore allows us to estimate disc quality by measuring IDP during flexibility testing.

Until biomechanical testing, the specimens were stored frozen in sealed triple polyethylene bags at $-20^\circ$C. For the test, specimens were thawed in a 4°C climate controlled room for at least 12 hours. Specimens were prepared by carefully

### TABLE 1. Specimens Used in This Study

| Test Group                        | Specimen ID | Disc Level | Age | Sex | Grade of Degree | Intrinsic Pressure, MPa | Pressure in Flexion, MPa | Pressure in Extension, MPa | Herniation                  |
|-----------------------------------|-------------|------------|-----|-----|-----------------|-------------------------|--------------------------|-----------------------------|------------------------------|
| Moderate/severe degeneration group| 1172        | L4–L5      | 57  | Male| 2               | 0.01                    | 0.14                     | 0.09                        | ...                          |
|                                   | 1188        | L2–L3      | 60  | Female| 2              | 0.02                    | 0.25                     | 0.25                        | After 20 cycles              |
|                                   | 1189        | L2–L3      | 59  | Male | 3               | 0.02                    | 0.18                     | 0.23                        | ...                          |
|                                   | 1189        | L4–L5      | 59  | Male | 2               | 0.0                      | 0.07                     | 0.02                        | ...                          |
|                                   | 1190        | L2–L3      | 64  | Male | 3               | 0.02                    | 0.01                     | 0.19                        | ...                          |
|                                   | 1221        | L2–L3      | 52  | Male | 2               | 0.05                    | 0.16                     | 0.22                        | ...                          |
| Mild degeneration group           | 1222        | L2–L3      | 31  | Female| 1              | 0.1                     | 0.39                     | 0.37                        | During flexibility test      |
|                                   | 1222        | L4–L5      | 31  | Female| 1              | 0.07                    | 0.41                     | 0.33                        | After 1000 cycles            |
|                                   | 1223        | L2–L3      | 49  | Male | 1               | 0.07                    | 0.29                     | 0.27                        | After defect creation        |
|                                   | 1223        | L4–L5      | 49  | Male | 1               | 0.08                    | 0.36                     | 0.29                        | After defect creation        |
|                                   | 1285        | L2–L3      | 51  | Female| 1              | 0.1                     | 0.34                     | 0.42                        | After 20,000 cycles          |
|                                   | 1285        | L4–L5      | 51  | Female| 1              | 0.07                    | 0.27                     | 0.3                         | After 20,000 cycles          |

The intradiscal pressure was measured in the intact state of each specimen.

The degree of disc degeneration was determined according to Wilke et al. using high quality radiographs from a Faxitron.

Mild degeneration equated to grade 1, moderate degeneration to grade 2, and severe degeneration to grade 3.
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stripping off soft tissue and muscle layers, thereby preserving all bony structures and ligaments. Subsequently, the cranial and caudal ends of the specimens were embedded into polymethylmethacrylate (PMMA, Technovit 3040, Heraeus Kulzer, Wehrheim, Germany). All biomechanical testing was performed at room temperature, and all specimens were sprayed with saline solution throughout the experiment to avoid dehydration and disintegration.

At the beginning of the experiment the specimens were tested in a custom-built spine tester (Figure 1A) to determine the flexibility (see subsequent text). Then a defect was created in the annulus to provoke a herniation. To create a “worst-case” scenario we chose a posterolateral box anulotomy measuring $6 \times 10$ mm (height × width) using a custom-made punch after a hemilaminotomy (Figure 2). A trial tool confirmed access to the disc. No nucleus was removed from the disc space. The correct orientation of the defect was controlled using fluoroscopy. After the creation of this defect, the flexibility test was repeated. If no herniation occurred with this flexibility test, the specimens were put in a dynamic testing machine to further provoke herniation. Complex cyclic loading was applied (see subsequent text) until a visible nucleus extrusion occurred (Figure 1B) or until we reached 100,000 load cycles.

If a herniation occurred, the extruded nucleus material was pushed back into the disc and the annular defect was closed with an annular closure device. We chose the Barricaid implant, which consists of a titanium anchor inserted below the end-plate of the adjacent vertebra, connected to a flexible, woven PET mesh placed inside the disc to seal the annulus internally (Figure 3A). The implantation was performed in accordance with the manufacturer’s surgical instruction manual, including use of a C-arm to guide the procedure (Figure 3B-D). Radiographs in lateral and anteroposterior direction documented the position of the implant directly after implantation and after each cyclic loading unit. After the defect was closed the dynamic test was repeated up to a new total of 100,000 cycles or until new extrusion of nucleus material occurred. Cyclic loading was paused after 20,000, 40,000, 60,000, and 100,000 loading cycles to inspect for extrusion of nucleus material, perform flexibility tests, and to obtain height measurements (Figure 1C) (see subsequent text).

Flexibility Testing

Flexibility testing (Figure 1A) was performed by applying pure bending moments continuously at a constant rate of $1.5^\circ/s$.

Cyclic Testing

Dynamic testing was performed in a servohydraulic material-testing machine (8871, Instron Wölpert GmbH, Darmstadt, Germany) (Figure 1B) to provoke the herniation and to apply long-term cyclic loading of the specimens after having implanted the Barricaid annular closure device. For this purpose the specimens were fixed with flanges to a custom rotating base mounted transversely, which rotated at $360^\circ/min$. This rotation base was shifted 30 mm laterally to apply an eccentric cyclic load. Load of the hydraulic piston was linearly increased to a preload of 100 N. Then a sinusoidal force that ranged between 100 and 600 N was applied at 5 Hz. The 30 mm of lateral shift acted as a lever arm, resulting in a maximum moment of 18 Nm.

Measurement of Disc Height

The measurements of disc height in the different states were also carried out in the servohydraulic material-testing machine.
motion of functional spine units under application of the pure bending moment was defined as RoM in 1 direction. The neutral position is the midpoint between the 2 intersection points defining the NZ.

For the height measurements and the flexibility data, statistical analyses were performed using the Wilcoxon signed-rank test between the intact state and the different conditions. Because this study was explorative, the P values were not corrected for multiple comparisons and thus only present trends.

**RESULTS**

The findings showed strong differences for the likelihood of a herniation based on degeneration.

In the specimen group with moderate/severe degeneration (degeneration grade 2 and 3) cyclic loading produced only 1 nucleus herniation even with the large defect. This extrusion motion of functional spine units under application of the pure bending moment was defined as RoM in 1 direction. The neutral position is the midpoint between the 2 intersection points defining the NZ.

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started after the first 20 loading cycles (Figure 4). The other specimens did not show signs of herniation after 100,000 load cycles. In this group, the specimens showed an intrinsic IDP value with a median of 0.02 MPa in the neutral position (0 Nm) (Table 1, Figure 5). In flexion, IDP increased up to a median of 0.15 MPa and in extension up to 0.2 MPa. Because a herniation could be produced in only 1 out of 6 specimens with moderate/severe degeneration, this group was not further investigated, therefore it cannot be considered as a “reliable herniation” group.

In the group with mild degeneration (degeneration grade 1) a disc prolapse occurred in all 6 specimens. In 2 segments, both from the same donor (#1223), simply the creation of the posterior defect caused an extrusion (Table 1). Another specimen showed the herniation during the initial flexibility test (#1222, L2–L3). In 1 specimen, extrusion occurred after only 1000 load cycles (#1222, L4–L5) and in the 2 others, after 20,000 cycles (#1285, L2–L3 and L4–L5). In this group, the intrinsic IDP showed a median value of 0.08 MPa in neutral position (0 Nm). Flexion and extension resulted in an almost symmetrical IDP increase up to median values of 0.35 MPa in flexion and 0.32 MPa in extension at the maximum bending moment of 7.5 Nm (Table 1, Figure 5). In comparison with the specimens of the moderate/severe degeneration group, the

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**Figure 6.** Change of disc height (median with minimum and maximum) of mild degeneration group after the anular defect, with the anular closure implant and after each load cycle unit. *P < 0.05 (Wilcoxon signed-rank test) status compared with intact.

**Figure 7.** RoM and NZ of the mild degeneration group (median with minimum and maximum). Data are normalized to the corresponding intact situation *P < 0.05 (Wilcoxon signed-rank test). + + P < 0.05 (Wilcoxon signed-rank test compared with defect). RoM indicates range of motion; NZ, neutral zone.
IDP response of the mild degeneration group was greater by approximately 50%. Median disc height loss after the anularotomy was about 0.6 mm. The anular closure device, which was only inserted in the reliable mild degeneration group, restored disc height to a remaining loss of 0.2 mm, which after cyclic loading disc height decreased again by a median of 1.1 mm (Figure 6).

With the implant in place, none of the 6 specimens showed a reherniation of nucleus material during cyclic loading. All implants stayed in place throughout the testing. The flexibility test revealed that in general the defect increased the RoM by approximately 25% in each loading direction (Figure 7). Implantation of the Barricaid device showed a slight trend to reduce the RoM and the NZ, except in extension. Implantation did not restore these values to the intact condition. Cyclic loading increased the flexibility of the specimens mainly due to viscoelastic effects.

DISCUSSION

With this study, we were looking for a reliable in vitro herniation model with human specimens, which would allow us to evaluate anulus closure techniques under cyclic loading conditions. We found that only mildly degenerated discs show a high extrusion risk. In these discs, the nucleus still behaves like a hydrostatic fluid, which should additionally be confirmed by IDP measurements. This process filters specimens that will produce a reliable nucleus extrusion, by showing that a high hydrostatic pressure is acting in the nucleus when applying load to the segment. The hypothesis was that if the disc generates higher pressures, it is less degenerated and is therefore likely to produce a herniation through the anular defect. This hypothesis was proven true, with nucleus extruding either immediately after the anulotomy or during flexibility or cyclic loading, resulting in a 100% rate of nucleus extrusion in specimens of the mild degeneration group. The prescreening for adequate IDP is therefore suggested for future studies of anular closure technologies. Furthermore, the mild degeneration group showed that the herniated nucleus material could be pushed back into the disc and the Barricaid device could prevent reherniation.

In contrast the moderate/severe degeneration group resulted, even after extensive cyclic loading, in only a single nucleus extrusion of the 6 tested specimens. Apparently, the nucleus does not tend to herniate frequently in discs between the ages of 55 and 65 because the tissue already is too fibrous, which is consistent with clinical data. The results of the moderate/severe degeneration group showed that degenerated or "older" specimens are not suitable for experiments with anulus closure devices. Therefore, the implant test has only been performed with the mild degeneration group where a herniation could be guaranteed.

A prior extrusion experiment that demonstrates the limitations of suture and gluing techniques incorporated the use of calf discs subjected to 4 to 24 Nm of loading. The use of young, healthy calf discs ensured adequate hydrostatic IDP generation and permitted the application of large applied moments. With this study we wanted to establish a method with human cadaveric discs, to provide a more anatomically relevant model to evaluate anular closure implants, which are designed for human applications.

To standardize the experiment a rectangular anular defect 6 mm tall by 10 mm wide was created, representing a worst-case scenario. Before the experiment, there was some conjecture that the defect size of 6 × 10 mm might have been too large for the implant, which would allow nucleus material to be extrude beside the implant. However, no clinically relevant amount of nucleus extrusion was observed. The anchoring technique seems to prevent migration under this kind of loading, as evidenced by the macroscopic view and radiographs.

A total of 100,000 test cycles were applied. Compared with the literature, this is a very high number of load cycles. Further increase of the number of cycles would result in artifacts due to autolysis processes. Previous experience shows that the entire experiment should not take longer than 20 hours.

A total of 100,000 test cycles with a frequency of 5 Hz were applied in every combination of flexion-extension and lateral bending in a continuous manner. It is recognized that 5 Hz may not represent herniation-generation behavior. The choice of a higher test frequency was a concession to balance the goal of applying a significant number of load cycles, whereas the human tissue was still viable (i.e., not dehydrated and not overly degraded due to temperature). Despite the limitation of loading rate, this method is standardized and reproducible, and has been previously published for other tests as a method that could provoke herniations.

It can be assumed that more than 100,000 cycles would probably lead to similar conclusions as we reach an asymptotic behavior as shown by the disc height change (Figure 6). This set-up with cyclic moments acting on the turning specimens causes complex loading conditions in all directions. The load varied between 100 N, which corresponds to the load on a human spine at rest, and 600 N, a load that occurs during sitting or standing. The resulting 18 Nm is assumed not to be destructive, but is likely significantly higher than during normal daily activities. Furthermore 10 to 12 Nm is referenced in ASTM F2423–05 Standard Guide for Functional, Kinematic and Wear Assessment of Total Disc Prostheses during functional loading, that is, normal daily activities.

Thus, the magnitude of 18 Nm represents loading that is 50% or higher.

Unfortunately, biological and physiological repair processes, which may occur in vivo cannot be simulated. Therefore, the situation in this in vitro setup can again be considered a worst-case scenario. Therefore, 100,000 cycles with 18 Nm applied at a frequency of 5 Hz can be considered as a good compromise and even exaggerate conditions of the first postoperative weeks to months.

Overall, this experiment helped to establish a herniation model with human specimens that reliably produced nucleus extrusion during cyclic loading, and it could be shown that the Barricaid device seems to prevent the nucleus from reherniating without migration of the implant, even in the presence of large anular defects and high cyclic loading.
CONCLUSION

Although today there are only a few technical solutions to prevent a reherniation of intervertebral disc, it can be speculated that new ideas will be developed. The reliability of this method suggests continuing investigations with different anulus closure methods as well as with nucleus replacement techniques in combination with anulus closure methods.

Key Points

- We established a human herniation model that reliably produced extrusion during cyclic loading.
- Reliable herniation is strongly dependent on the degree of disc degeneration and the quality of the nucleus material as demonstrated by IDP measurements.
- Using this worst-case model, anulotomy, and loading led to herniation and disc height reduction, which was almost restored with the Barricaid implant.
- In no case was a reherniation or implant migration visible after 100,000 load cycles.

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