Anterior spinal instrumentation combining a prosthetic disc nucleus with a flexible stabilization device: Manufacture and use in intervertebral disc repair

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Abstract. Artificial disc replacement alone is unable to completely cure cervical degenerative diseases; thus, a stabilization device markedly improves patient recovery. In order to meet this requirement, an anterior spinal instrumentation combining a prosthetic disc nucleus with a flexible stabilization device (ASI combining PDN/FD) was developed. An artificial disc was designed and manufactured using polyvinyl alcohol hydrogel (PVA-H) with a repeated freeze-melting technique, and subsequently the dehydration and swelling properties of the PVA-H were investigated. A canine animal model was then used to compare the differences in the degeneration of cervical discs adjacent to the operative segment with PDN/FD against a plate fixation system, without the interferences of brace intensity, which was ensured by pressure monitoring the dog's intervertebral disc adjacent to operative segments. The *in vivo* results demonstrated a clear decrease in the degeneration of the adjacent disc with the use of PDN/FD as compared with the plate fixation system. In conclusion, PDN/FD may offer a promising method for the treatment of cervical degenerative disease.

Introduction

With the aging of the population and increase in desk jobs, cervical disc degenerative diseases have become increasingly common and affect the patients' quality of life (1). These diseases occur as a result of the degeneration of the cervical discs. When degenerative changes occur, the moisture content of the cervical disc nucleus markedly decreases, which results in the loss of viscosity and flexibility (1). These alterations then result in decreased clearance between the cervical vertebrae, small joint disorder, cervical instability, cervical biomechanical disturbance and abnormality of the cervical structure, all of which can cause clinical symptoms and physical signs, including neck and shoulder pain and arms paralysis (2).

Currently, the two most common methods of treating cervical disc degenerative diseases caused by the pathology described earlier include removal of the lesion and intervertebral bone-graft fusion with internal fixation (3). The curative effects of these techniques have been demonstrated; however, each technique presents certain disadvantages (4). More specifically, removal of the lesion results in decreased clearance between cervical vertebrae and cervical instability. In addition, spinal fusion with rigid devices, including steel plates, bolts and fusion cages, accelerates the degeneration of adjacent cervical vertebrae and facet joints (3,4). This accelerated degeneration is a result of alterations in the normal physiological shape and biomechanical structure of the cervical spine (4).

Accordingly, the structure and biomechanics of cervical discs and the disc nucleus have been extensively investigated. Prosthetic disc nuclei and artificial cervical discs have been developed in order to treat cervical diseases in recent years (5). In 1966, Fernström (6) described the implantation of a stainless steel ball as a treatment for cervical disease. However, this technique had certain disadvantages, such as the loss of height between the discs when the implanted ball sank into the disc over time. In the past 40 years, researchers have made rapid progress in the fields of material science and biomechanics. Artificial disc replacement and prosthetic disc nucleus replacement are now effective procedures to treat cervical disc degenerative diseases (7,8). These techniques can maintain the normal physiologic function, preserve the height and increase the total volume between the cervical discs, support compressive forces and relieve the symptoms of spinal disease (9,10). The numerous advantages of prosthetic disc nucleus replacement include a minimally invasive surgery, low associated costs and safe procedure (10).

There are two types of internal fixation, flexible and rigid (11). Rigid fixation solves the problem of spinal instability; however, it is associated with problems such as osteoporosis of the adjacent vertebrae, spinal canal stenosis, facet joint disorders and adjacent segment degeneration (11). Biomechanical analysis has demonstrated that these symptoms are caused by excessive rigidity of the internal fixation (12).

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Thus, degradable internal fixation systems have also been developed. However, these materials have several issues, including the short duration of support, production of fragments and lack of mechanical strength (12). Recently, flexible stabilization devices have been designed by Strauss *et al* (11) and Leahy *et al* (12). Flexible stabilization devices consisting of woven fabrics of elastic polyester have been used to stabilize the zygapophysial joints via a pedicle screw-lamina hook system. Consequently, a flexible stabilization device is preferable to a rigid device since it provides improved mobility and quality of life following surgery. However, flexible stabilization devices require a two-step process, involving an initial implantation of the prosthesis and subsequently placement of the stabilization system. This two-step process increases the difficulty of the procedure and lengthens the surgery duration (11,12).

Based on the aforementioned developments, an anterior spinal instrumentation system combining a prosthetic disc nucleus with a flexible stabilization device (ASI combining PDN/FD) was developed in the present study and examined by *in vivo* experiments. The main advantages of PDN/FD include the following three features: i) The prosthetic disc nucleus has good biomechanical properties and can replicate the physiological function of the disc nucleus; ii) the wing-like weave functions as an artificial ligament, which increases the stability of the adjacent vertebrae; and iii) the wing-like weave helps maintain the location of the prosthetic disc nucleus, preventing the nucleus from breaking off to the spinal canal and aiding early mobilization. There is currently no measurable standard to analyze the results of PDN/FD surgery. Therefore, a novel evaluation method was established in the current study, involving pressure measurement combined with imaging analysis and histology. A comparison of the adjacent intervertebral disc degeneration in dogs treated with PDN/FD compared with those treated with a plate fixation system demonstrated reduced degeneration in the PDN/FD group. Thus, this is a promising technique for the treatment and repair of degenerating cervical discs.

Materials and methods

Materials. Polyvinyl alcohol (PVA) type 1799, with a molecular weight of 74,800-79,200 and an alcoholysis degree of 99.9%, was purchased from Beijing Huaer Co., Ltd. (Beijing, China). Ketamine and penicillin were obtained from the 309th Hospital of PLA (Beijing, China). The experiments of the present study were approved by the Ethics Committee of the 309th Hospital of PLA.

Implanted materials. The PDN/FD consisted of an artificial alar ligament, a 2.5-mm connecting ligament and a prosthetic disc nucleus composed of a core and surrounding material (Fig. 1). The alar ligament, connecting ligament and core-surrounding material were composed of polyethylene with an ultra-high molecular weight supplied by the College of Textiles, Tianjin Polytechnic University (Tianjin, China), while the core was composed of PVA hydrogel. In order to allow normal physiological activities, a 2-mm extension was made for the alar ligament. The prosthetic disc nucleus was surrounded with a radiopaque thread supplied by the College of Textiles, Tianjin Polytechnic University (Tianjin, China). Furthermore, a plate fixation system was used in the control group, which consisted of a titanium plate with 2-4 holes and 5-10 titanium alloy screws, and was supplied by Beijing Sinotech Medical Supplies Co., Ltd. (Beijing, China).

Manufacture of PVA hydrogel. PVA was dissolved in water in a high-pressure container at a temperature of 90˚C for 6 h. The solution was then cast into a mold and frozen at -20˚C for 6-12 h. Next, the frozen PVA hydrogel was melted by keeping it at room temperature for 1-2 h. This freeze-melt process was repeated three times, and the frozen solution was subsequently vacuum dehydrated for 8 h. Finally, the sample was placed in sterile water at 37˚C for 2 days to achieve saturation and to form a hydrogel.

Measurement of dehydration and swelling of PVA hydrogel. The prepared PVA hydrogel was accurately weighed and denoted by W_0, while its volume was measured and denoted by V_0. Next, the PVA hydrogel was placed into an electro-thermostat device at a temperature of 25˚C, and its weight (W_t) and volume (V_t) were measured at different time points (denoted by t) until they were stable. The dehydration ratio (W_r) and volume shrinkage percentage (Q) of the PVA hydrogel were calculated according to equations 1 and 2, respectively.

$$W_r = \frac{W_t}{W_0} \times 100\% \quad (1)$$

$$Q = \frac{V_t}{V_0} \times 100\% \quad (2)$$

When a constant weight was achieved, the dehydrated PVA hydrogel was weighed (W_d) and then placed in deionized water. The swelling ratio (S_{wt}) was calculated according to equation 3.

$$S_{wt} = \frac{W_t - W_d}{W_d} \times 100\% \quad (3)$$

Animal grouping. The healthy dogs were selected as the animal model in the present study. In total, 18 healthy mixed-breed dogs (age, 1.5-2.5 years; 9 males and 9 females; body weight, 20.0-30.0 kg) were maintained in a temperature controlled room (temperature, 20˚C; humidity, 45%) with a 12-h light/dark cycle and free access to water and food) at the Animal Experiment Center at the 309th Hospital of PLA. The dogs were divided into two groups (n=9 in each group), with dogs in Group A receiving PDN/FD and dogs in Group B receiving a plate fixation system.

Surgical method. Dogs were anesthetized with an intravenous injection of ketamine (10 mg/kg), and placed in a supine position. An 1-cm incision was made on the left side of midline, and soft tissues were cleared from the anterior aspect of the vertebral body. The exposed centrum and annulus fibrosus were bluntly dissected following sharp dissection of the prevertebral fascia. The pressure transducer was not connected to the spinal needle until the centrum was confirmed with X-rays obtained with a C-arm device. Next, a multifunctional

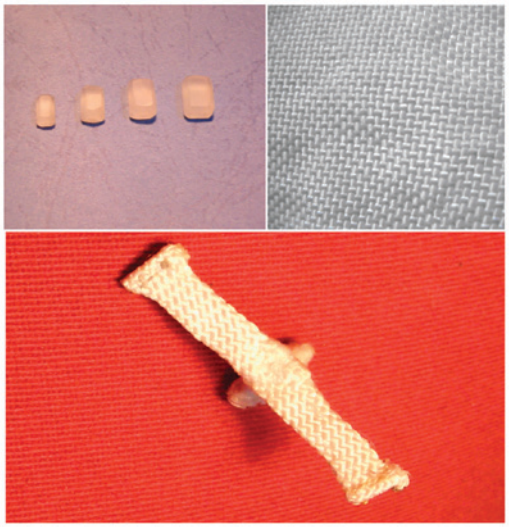

Figure 1. Anterior spinal instrumentation system combining a prosthetic disc nucleus with a flexible stabilization device.

patient monitor (Dash 4000; GE Healthcare, Little Chalfont, UK) was connected for invasive manometry measurement. The system was filled with lactated Ringer's solution (College of Textiles, Tianjin Polytechnic University). A lumbar spinal needle was inserted vertically at C4/5 to record the pressure, with a horizontal pressure setting of zero. Discectomy of C3/4 was performed subsequent to cutting the annulus fibrosus. In Group A, the PDN/FD was placed with a titanium screw fixing each end of the alar ligament to the centrum, whereas a plate fixation system was placed in Group B. Following the implant placement, the pressure at C4/5 was recorded again with the method described earlier. The difference between the preoperative and postoperative pressures was calculated as the brace pressure. To study without the interferences of brace intensity, the pressure in the dog's intervertebral disc adjacent to operative segments was monitored and the two groups were maintained to the same brace pressure at 2 mmHg. Subsequently, the incision was securely sutured after flushing with streptomycin, and the dogs received 1.6 million units of penicillin intramuscularly prior to waking from anesthesia and once daily for the following 3 days. Wound healing, ambulatory state, diet and complications were monitored.

Imaging. Lateral anteroposterior and flexion-extension radiographs were obtained prior to surgery, in order to rule out the possibility of preexisting degenerative disease, and at 6 months after surgery. Radiographs were analyzed to determine any alterations in the intervertebral height, cervical physiological curve and vertebral position. At the same time, magnetic resonance imaging (MRI) was performed to evaluate the degenerative changes at C2/3 because C2/3 was adjacent to C3/4 (operated segment) and C4/5 disc was only measured in the operation. This was performed according to the Pearce standard (13).

Histopathology. Animals were euthanized and the disc at C2/3 was collected 6 months after surgery. Disc specimens were observed grossly for evidence of inflammation and degeneration of the annulus fibrosus and end plate. Briefly, the C2/3 sample was decalcified in 10% nitric acid and embedded in paraffin wax following fixation in formaldehyde (20˚C) solution for 72 h. Next, 4-mm sections were prepared and stained with hematoxylin and eosin. The degeneration level of C2/3 was classified according to the scale described by Lou *et al* (14), as follows: Level 1, numerous matrix components, with thin and ordered collagenous fibers; level 2, few matrix components, with thick and disordered collagenous fibers; level 3, twisted, thick and disordered tufted collagenous fibers; and level 4, collagenous fibers more disordered and gathered into a mass as indicated in a previous study by Lou *et al* (14).

Statistical analysis. Data were analyzed using statistic software of SPSS 22.0 (IBM Corp., Armonk, NY, USA). The degree of degeneration of the intervertebral disc adjacent to the operative segment (C2/3) was evaluated according to the Pearce standard. Histological differences were evaluated according to degeneration level. Pearce levels and degeneration levels in group A and B were evaluated with a Student's t-test.

Results

Dehydration and swelling properties of the PVA hydrogel. Dehydration of the PVA hydrogel occurred mainly in the initial 12 h, with the mass and volume decreasing by 33.7 and 50.7%, respectively. The final dehydration ratio was 28.8%, while the volume shrinkage percentage was 26.3%. Furthermore, PVA hydrogel swelling was mainly observed in the initial 24 h, with the swelling ratio increasing by a maximum of 84.7%, and subsequently trending toward stability. At 72 h, the hydrogel was completely swollen, with the mass increasing to 112.7% of the PVA hydrogel mass prior to dehydration.

Imaging and histopathology results. Instability was defined as a difference in angulation of >20˚ between the flexion and extension radiographs at the intervertebral disc space. According to this definition, there were four cases of C2/3 instability in Group B (44.4%), while no cases of instability were observed in Group A, as demonstrated in radiograph and MRI scan results (Figs. 2 and 3). At 6 months after surgery, the mean Pearce level of C2/3 in Group A was 1.89, which was markedly higher compared with the Pearce level of 3.22 in Group B ($P<0.05$). Similarly, the degeneration degree of C2/3 in Group A was 1.67, which as significantly lower compared with the level of 2.78 in Group B ($P<0.05$; Tables I and II).

Discussion

In the present study, the core of the prosthetic disc nucleus was composed of PVA hydrogel, which possessed good water absorbency, with a water content of 70-80% in the hydrated state, close to the normal human physiological conditions. Swelling PVA hydrogel was selected as the core of the prosthetic disc nucleus in order to reduce trauma and risk. A previous study (15) have indicated that prosthetic disc nuclei should not exhibit excessive creep deformation and should recover their height well once external forces are withdrawn,

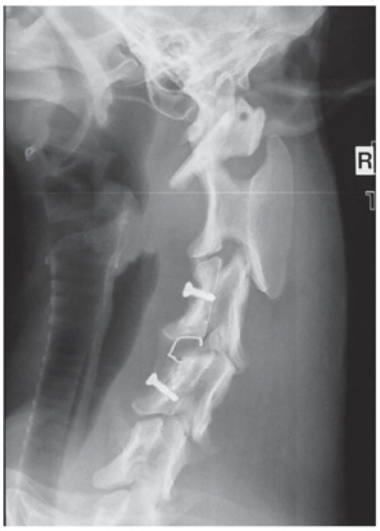

Figure 2. Radiograph of a dog from group A implanted with an anterior spinal instrumentation system combining a prosthetic disc nucleus with a flexible stabilization device.

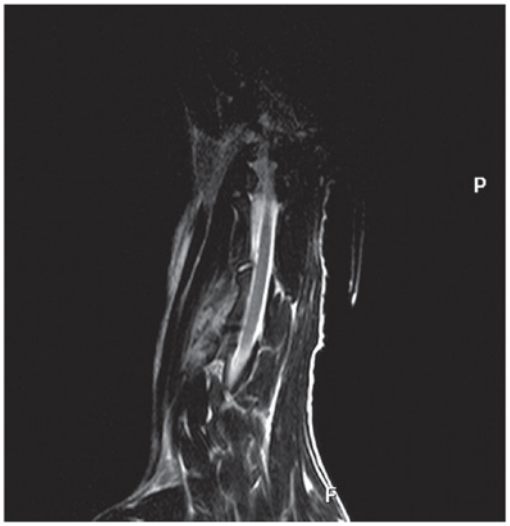

Figure 3. Magnetic resonance imaging scan of a dog from group A implanted with an anterior spinal instrumentation system combining a prosthetic disc nucleus with a flexible stabilization device (C2/3 Pearce level 1).

Table I. C2/3 disc degeneration demonstrated according to the Pearce level of the dogs.

Pearce level	Group A, n	Group B, n	Subtotal, n
1	3	0	3
2	4	1	5
3	2	5	7
4	0	3	3
5	0	0	0
Mean	1.89	3.22	2.56
Total	9	9	18

Comparisons were conducted with the Student's t-test, group A vs. group B was significant $P<0.05$.

Table II. Histological differences were evaluated according to the level of C2/3 disc degeneration in dogs from the two groups.

Degeneration level	Group A, n	Group B, n	Subtotal, n
1	4	0	4
2	4	3	7
3	1	5	6
4	0	1	1
Mean	1.67	2.78	2.22
Total	9	9	18

Comparisons were conducted with the Student's t-test, group A vs. group B was significant ($P<0.05$).

within the range of human intervertebral disc biomechanics. Furthermore, 10-million-cycle fatigue testing of PVA hydrogel at 4 Hz frequency demonstrated that the height and elastic modulus were not altered significantly (15).

The degeneration of adjacent intervertebral disc is affected by various factors, including the brace pressure. In the present study, the difference between preoperative and postoperative pressures was calculated as the brace pressure. Significant positive correlations were detected between the Pearce level, degeneration level and brace pressure in each group. Accordingly, it is suggested that pressure alterations affecting the degeneration of adjacent cervical discs must not be ignored. Excessively increased pressure in the disc adjacent to the operated segment may result in the degeneration of that segment. Therefore, attention should be paid not only to the reconstruction of cervical lordosis and stability, but also to the accurate distraction forces during surgery. Pressure monitoring of the adjacent disc during surgery reduces the risk of future degeneration. In the current study, there was no significant differences in the brace pressure between Groups A and B. As a consequence, the effect of implanted materials was evaluated directly without the confounding factor of distraction force.

Anterior bone-graft fusion and internal fixation have commonly been used to restore the disc height, lessen the cervical facet joint loading and stabilize the fusion segments (15). However, bone-graft fusion disturbs the normal mechanical transmission of the cervical vertebrae and increases the load on adjacent segments, resulting in stress concentration and potentially accelerating the degeneration of adjacent segments (16). Treatment for joint disease has altered from fusion to artificial joint replacement, with artificial disc replacement (including whole disc replacement and prosthetic disc nucleus replacement) being performed in place of spinal fusion (17). Prosthetic disc nucleus replacement has certain advantages over the traditional procedure, including reconstruction of the physiological function units, decrease of the load on adjacent segments and reduction of the likelihood of degeneration. The present study confirmed that the Pearce

levels and degeneration levels in Group A that was treated with PDN/FD were significantly lower in comparison with those of Group B, in which a plate fixation system was used. Evidently, PDN/FD prevented the degeneration of adjacent segments more effectively as compared with the plate fixation system. In addition, PDN/FD restored the normal intervertebral height and the physiological annulus fibrosus. At the same time, the synthetic alar ligament strengthened the anterior longitudinal ligament, which reinforced the endogenous factors promoting cervical stability, avoided stress concentration in the bilateral facet joints and contributed to the recovery of the physiological curvature.

As previously reported (18), lumbar intervertebral discs are in a hydrostatic state due to their diffluent matrix composed of proteoglycan protein and water. As a result, the internal pressure of lumbar intervertebral discs can be measured. Furthermore, there are no significant pressure differences among different lumbar intervertebral discs (18). Due to the hydrostatic property of cervical intervertebral discs, intervertebral disc manometry was used in the present study to quantify brace pressure to compare the impact of different brace pressure on adjacent segments. However, small absolute values and inconsistencies between intraoperative and postoperative positioning led to measurement errors. Therefore, in the current study, the pressure differences were measured to avoid systematic errors and to minimize measurement errors in the absolute values. However, this manometry technique can injure the normal cervical intervertebral disc and accelerate its degeneration. To address this problem, the adjacent segment below the operative segment, which is relatively resistant to deterioration, was used in measurements in the present study, while the easily deteriorated segment above the operated segment was selected for observation. Furthermore, one-step surgery was performed in order to reduce duplication surgery, avoiding further injury. Nevertheless, intervertebral disc manometry is in its initial stages of study. Various issues remain to be clarified, including the influence of pressure changes on the degeneration in adjacent segments.

In conclusion, the present study demonstrated that disc degeneration may be decreased by using ASI combining PDN/FD compared with plate systems. PDN/FD may offer a promising method for the treatment of cervical disc degenerative diseases.

Competing interests

The authors declare that they have no competing interests.

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