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Original Article

Effect of anterior cervical discectomy and fusion on adjacent segments in rabbits

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Abstract: This study is to investigate the effect of anterior cervical discectomy with internal fixation and fusion at different levels on adjacent segments in rabbits. Sixty New Zealand rabbits were randomly divided into four groups, one control group and three model groups, with 15 in each group. Each group underwent anterior cervical internal fixation and fusion at C3-4, C4-5, and C5-6 levels respectively. X-ray film was examined three, six and nine months after fusion to observe the changes in intervertebral space and endplate of adjacent segment. Immunohistochemistry was utilized to evaluate the effects of different fusion methods on adjacent segments of spine. As time went by, in model groups, the majority of cartilage endplates were calcified, as examined by X-ray. Immunohistochemical results of the intervertebral disc showed that the expression levels of collagen type II in nucleus pulposus were decreased significantly, while the expression levels collagen type I in annular fibrosus were increased. And collagen type I tends to replace collagen type II gradually in nucleus pulposus as time goes by. The change in collagen between upper and lower adjacent segments at C3-4 and C4-5 showed no statistical significance after fixation and fusion ($p > 0.05$). But for C5-6, the change showed statistical significance ($p < 0.05$). Cervical internal fixation and fusion can induce intervertebral disc degeneration of adjacent segment in rabbits, and cervical internal fixation and fusion operated at different levels may result in different effects on adjacent segments of cervical intervertebral disc.

Keywords: Cervical vertebra, adjacent segment, internal fixation and fusion, intervertebral disc

Introduction

Spinal fusion has been widely applied in clinical practice, and plays an extremely important role in the treatment of spinal trauma, degenerative disease, congenital spinal deformity and spinal tuberculosis. However, after spinal fixation and fusion, some patients were found to have adjacent segment degeneration (ASD) [1-3] gradually, and even adjacent segment disease. In recent years, scholars have noticed that the spinal fusion can induce adjacent segment degeneration and there is an upsurge of investigating the retention of spinal motion segment. They used new surgical approaches and new methods of artificial nucleus replacement and artificial disc replacement. Meanwhile, many scholars carried out in-depth study on adjacent segment degeneration after fusion from the biomechanical perspective after follow-up observation of clinical cases. But there is still a lack of systematic research in animal models, and the relationship between spinal fusion and adjacent segment degeneration is still controversial. Some people think that the ASD is likely to be the natural progression of vertebral degeneration [4-7]. By observing the effect of spinal fusion on adjacent segment degeneration, we can have a deeper understanding of its pathological process in order to further improve the surgical effect, and can plan the conditions before treatment. Therefore, in this study, we attempted to establish an animal model of cervical fusion, with which the effect of anterior cervical discectomy and fusion (ACDF) of single segment at different levels on adjacent segments of cervical disc in rabbits and its laws were prospectively investigated, and the mechanism of this change was explored.

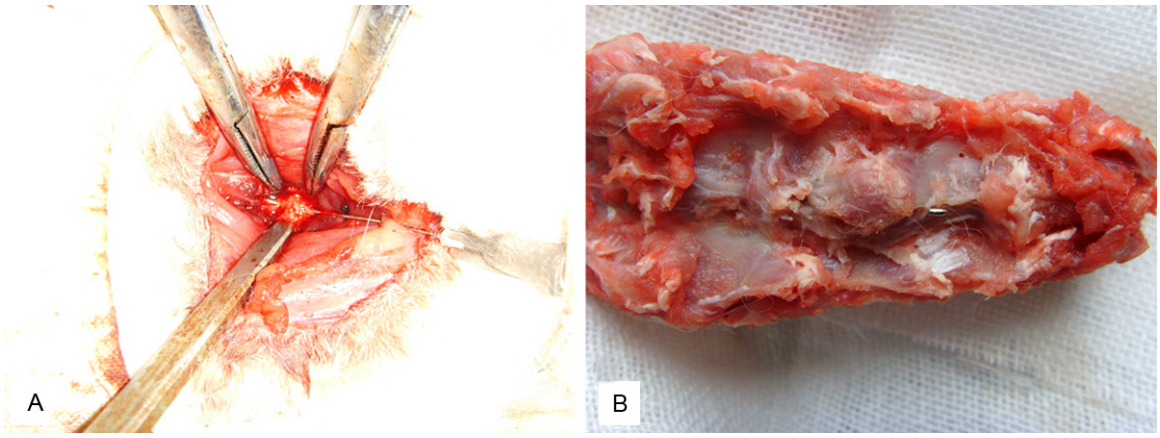

Figure 1. A: Anterior inter-body fusion and fixation (surgical approach), B: Segmental bone connection after fusion and fixation.

Materials and methods

Sixty male and female clean New Zealand white rabbits, aged from 1.5 to 2 months, weighing 1.5~2.0 Kg, were randomly divided into four groups, one control group and three experimental groups, with 15 in each group.

Study design

Surgical approach and postoperative care

The animals underwent the surgical procedure under intravenous anesthesia with 40% urethane (1 ml/kg). The anterior part of the neck and iliac crest was prepped in a sterile fashion. Iliac crest incision of about 2 cm was made layer by layer up to the iliac crest. Due to the presence of iliac crest cartilaginous cap, subperiosteal dissection was performed to expose the iliac outer plate, appropriate amount of outer plate and cancellous bone was taken for standby use, bone wax was used to stop bleeding, and the incision was closed by sutures. The anterior cervical skin was prepared, sterilized with 75% ethanol and covered with a surgical towel. Then, an incision was made of about 4 cm in the anterior neck via a midline right-sided approach into the carotid sheath, trachea and esophagus sheath, reaching in front of the vertebral body, through where ran an anterior vertebral artery. Model group one: The blood vessels were positioned at the C1-2 space, and ligated by sutures at the C3-4 levels. The longus colli muscle and anterior longitudinal ligament were dissected in the midline, and the C3/4 intervertebral disc was exposed. Anterior discectomy at the C3/4 levels was performed. The endplates were uniformly shaved down to bleeding bone. Autologous tricortical iliac crest bone graft were inserted uniformly into the intervertebral space. First, a hole was punctured with a 7G syringe, from the C3 vertebrae through the space to the C4 vertebrae, into the C4 vertebrae. Then, a triangular needle (9 × 27) was inserted into the C4 vertebrae through the hole channel, the C3-4 vertebrae was fixed (**Figure 1A**), and excessive pintail was cut off. Finally, the wound was irrigated with normal saline and the longus colli muscle was reapproximated with sutures to prevent pintail from damaging esophagus, the subcutaneous tissue and the skin were reapproximated with sutures, and a soft bandage was applied to the neck. Model groups two and three: Internal fixation and fusion were performed at C4/5 and C5/6 levels respectively with the same method mentioned above. Control group: Also under anesthesia, intervertebral disc was exposed, but not removed, without internal fixation and fusion, and closed with sutures layer by layer. After surgery, rabbits were raised in the cages. All rabbits were housed one per cage and fed diet and water ad libitum. Their neurological conditions and general health were checked each day.

X-ray examination

Three months after surgery, rabbits from each group were examined by X-ray. Those with inter-body fusion were included in the study while those without inter-body fusion were excluded.

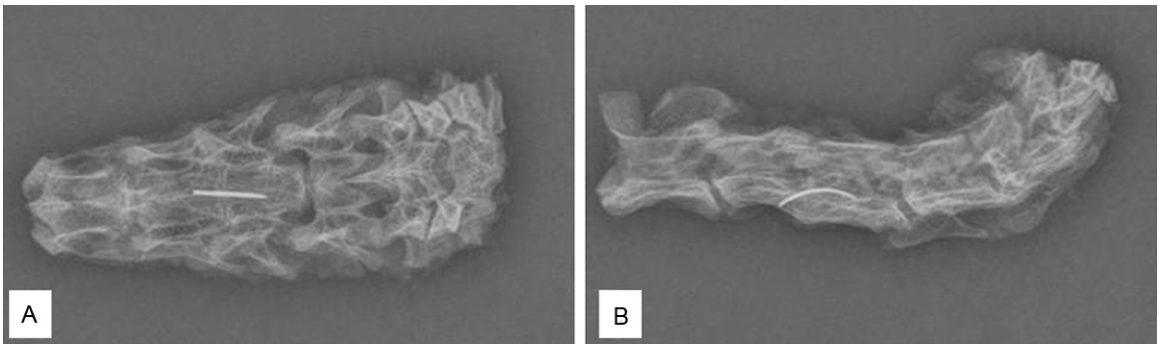

Figure 2. After anterior inter-body fusion and fixation, anteroposterior and lateral X-ray films showed: fixed intervertebral segment disappeared through the trabecular bone, and vertebrae were fused into one.

Then New Zealand White rabbits under the same conditions were additionally taken to the surgery in order to ensure 15 in each group for research. X-ray film was examined for rabbits from each group three, six and nine months after fusion to observe the changes in intervertebral space and endplate of adjacent segment. Then rabbits were sentenced under anesthetic overdose. Immunohistochemistry was utilized to evaluate the effects of different fusion methods on adjacent segments of spine.

Immunohistochemical analysis

Immunohistochemical analysis was made by using the conditions recommended by Wuhan Boster Biotech Development Company combined with the experimental methods the Department of Pathology, Yijishan Hospital Affiliated to Wannan Medical College. Type I collagen, type II collagen polyclonal antibody kits and other immunohistochemical reagents were purchased from Wuhan Boster Biotech Development Company. For each section, five non-overlapping high-power fields (10 × 40 times) were randomly counted. The total number of stained cells was divided by 5 to obtain the average number of positive cells of type I and II collagen under each high power field for statistical analysis.

Statistical analysis

Data were analyzed using SPSS 11.0 statistical software. The levels were compared between the control group and each treatment group using one-way ANOVA and LSD method. Pairwise comparison was made among groups with the q-test. For each group, paired t-test comparison was made between the two samples of upper and lower adjacent segment.

Results

Failure parameters and complications

In this study, wound infection occurred in 2 cases, including 1 in C3-4 and C5-6 group respectively. In order to avoid the influence on the results, these two cases were excluded, and New Zealand white rabbits under the same conditions were additionally taken to the surgery. Within one month after surgery, 3 cases died of unknown reasons, including 1 in control group, C3-4 group, and C4-5 group respectively. Then, these three cases were excluded, and New Zealand White rabbits under the same conditions were additionally taken to the surgery. And no deaths occurred since then. 8 cases without fusion, including 2 in C3-4 group, 3 in C4-5 group, and 3 in C5-6 group, were excluded, and New Zealand White rabbits under the same conditions were additionally taken to surgery.

A total of 73 New Zealand white rabbits were used in this study, 57 of which underwent fusion and internal fixation. These 57 cases included 2 cases with incision infection and 2 death cases, which were excluded and could not be observed further for the presence of fusion, and 53 cases, which were observed continuously and found to have fusion in 45 cases. Upper and lower fused vertebral segments were fixed (**Figure 1B**) with a fusion success rate of 84.9%.

Radiographic results

X-ray film showed: no significant changes in cartilage endplate were observed in the control group and the experimental groups after three months, but bone healing was seen in the fusion and fixation segments in experimental

Table 1. Expression of collagen I in annulus fibrosus in the upper and lower adjacent segments at each time point of each group (X ± S)

Surgery group	Segment	Number (n)	Annulus Collagen I expression (X ± S, n = 5)		
			3 months (5)	6 months (5)	9 months (5)
Control	Upper	15	15.4 ± 1.34	17.0 ± 1.22	18.8 ± 1.30
	Lower	15	15.6 ± 1.34	17.2 ± 1.10	19.0 ± 1.22
C3-4	Upper	15	16.8 ± 1.10	18.8 ± 1.30	21.0 ± 1.22
	Lower	15	17.0 ± 1.22	19.0 ± 1.22	21.2 ± 1.10
C4-5	Upper	15	16.6 ± 1.14	18.6 ± 1.34	20.8 ± 1.10
	Lower	15	17.2 ± 1.10	19.2 ± 1.30	21.4 ± 1.14
C5-6	Upper	15	16.2 ± 1.30	18.2 ± 1.10	20.4 ± 1.34
	Lower	15	17.4 ± 1.52	19.4 ± 1.34	21.6 ± 1.52

Note: There was no difference between groups at three months ($P > 0.05$), but statistically significant difference at six months and nine months between the surgery groups and the control group was ($P < 0.05$), and statistically significant difference at different time periods among surgery groups ($P < 0.05$). Paired T test was performed on adjacent upper and lower segments, and the results showed that there was statistically significant difference in the C5-6 group ($P < 0.05$), but no difference in other groups ($P > 0.05$).

Table 2. Expression of collagen I in nucleus pulposus cells in the upper and lower adjacent segments at each time point of each group (X ± S)

Surgery group	Segment	Number (n)	Nucleus pulposus cells Collagen I expression (X ± S, n = 5)		
			3 months (5)	6 months (5)	9 months (5)
Control	Upper	15	3.0 ± 1.22	4.6 ± 1.14	6.4 ± 1.14
	Lower	15	3.2 ± 1.30	4.8 ± 1.10	6.6 ± 1.34
C3-4	Upper	15	4.4 ± 1.14	6.4 ± 1.52	8.6 ± 1.14
	Lower	15	4.6 ± 1.14	6.6 ± 1.34	8.8 ± 1.10
C4-5	Upper	15	4.2 ± 1.10	6.2 ± 1.30	8.8 ± 1.10
	Lower	15	4.8 ± 1.10	6.8 ± 1.30	9.0 ± 1.22
C5-6	Upper	15	3.8 ± 1.30	5.8 ± 1.10	8.0 ± 1.22
	Lower	15	5.0 ± 1.22	7.0 ± 1.22	9.2 ± 1.10

Note: There was no difference between groups at three months ($P > 0.05$), but statistically significant difference at six months and nine months between the surgery groups and the control group was ($P < 0.05$), and statistically significant difference at different time periods among surgery groups ($P < 0.05$). Paired T test was performed on adjacent upper and lower segments, and the results showed that there was statistically significant difference in the C5-6 group ($P < 0.05$), but no difference in other groups ($P > 0.05$).

group (**Figure 2A**, **2B**). After six months, slight sclerosis of cartilage endplate was visible in the experimental groups. No significant differences were found between the upper and lower adjacent segments. No cartilage endplate sclerosis was found in the control group. After nine months, the experimental groups showed cartilage endplate sclerosis with increased density, and no significant difference between the upper and lower adjacent segments. The control group showed no endplate cartilage sclerosis.

Immunohistochemistry

Type I and II collagen expression showed brown staining granules in the cytoplasm with focal or diffuse distribution. The statistical results of immunohistochemical staining were shown in **Tables 1-4**. Difference was not statistically significant between three months and six months, as well as between six months and nine months in the control group ($P > 0.05$). Difference was statistically significant differences between three months and six months, as well as between six months and nine months in the experimental groups ($P < 0.05$). And there was also statistically significant difference in 6 months and 9 months between the experimental group and the control group ($P < 0.05$). Paired t test was performed on adjacent upper and lower segments. C3-4 group or C4-5 group showed no statistically significant difference in adjacent upper and lower segments ($P > 0.05$).

Table 3. Expression of collagen II in annulus fibrosus in the upper and lower adjacent segments at each time point of each group (X ± S)

Surgery group	Segment	Number (n)	Annulus Collagen II expression (X ± S, n = 5)		
			3 months (5)	6 months (5)	9 months (5)
Control	Upper	15	9.8 ± 1.10	8.2 ± 1.10	6.4 ± 1.14
	Lower	15	9.6 ± 1.34	8.0 ± 1.22	6.2 ± 1.30
C3-4	Upper	15	8.4 ± 1.14	6.4 ± 1.34	4.2 ± 1.10
	Lower	15	8.2 ± 1.10	6.2 ± 1.30	4.0 ± 1.22
C4-5	Upper	15	8.6 ± 1.14	6.6 ± 1.52	4.4 ± 1.34
	Lower	15	8.0 ± 1.22	6.0 ± 1.22	3.8 ± 1.30
C5-6	Upper	15	9.0 ± 1.22	7.0 ± 1.22	4.8 ± 1.10
	Lower	15	7.8 ± 1.30	5.8 ± 1.10	3.6 ± 1.34

Note: There was no difference between groups at three months ($P > 0.05$), but statistically significant difference at six months and nine months between the surgery groups and the control group was ($P < 0.05$), and statistically significant difference at different time periods among surgery groups ($P < 0.05$). Paired T test was performed on adjacent upper and lower segments, and the results showed that there was statistically significant difference in the C5-6 group ($P < 0.05$), but no difference in other groups ($P > 0.05$).

Table 4. Expression of collagen II in the nucleus pulposus cells in the upper and lower adjacent segments at each time point of each group (X ± S)

Surgery group	Segment	Number (n)	Nucleus pulposus cells Collagen II expression (X ± S, n = 5)		
			3 months (5)	6 months (5)	9 months (5)
Control	Upper	15	14.2 ± 1.30	12.6 ± 1.14	10.8 ± 1.30
	Lower	15	14.0 ± 1.22	12.4 ± 1.14	10.6 ± 1.34
C3-4	Upper	15	12.8 ± 1.10	10.8 ± 1.30	8.6 ± 1.14
	Lower	15	12.6 ± 1.52	10.6 ± 1.34	8.4 ± 1.14
C4-5	Upper	15	13.0 ± 1.22	11.0 ± 1.22	8.8 ± 1.10
	Lower	15	12.4 ± 1.52	10.4 ± 1.34	8.2 ± 1.10
C5-6	Upper	15	13.4 ± 1.14	11.4 ± 1.52	9.2 ± 1.30
	Lower	15	12.2 ± 1.10	10.2 ± 1.30	8.0 ± 1.22

Note: There was no difference between groups at three months ($P > 0.05$), but statistically significant difference at six months and nine months between the surgery groups and the control group was ($P < 0.05$), and statistically significant difference at different time periods among surgery groups ($P < 0.05$). Paired T test was performed on adjacent upper and lower segments, and the results showed that there was statistically significant difference in the C5-6 group ($P < 0.05$), but no difference in other groups ($P > 0.05$).

In the C5-6 group, degeneration was greater in the adjacent lower segment than the adjacent upper segment, and the difference was statistically significant ($P < 0.05$).

Discussion

ACDF and ASD

Spinal fusion has become the standard therapy for many spinal diseases. But over time, the clinical follow-up and radiologic examination reveal the occurrence of ASD, which has drawn our widespread concerns. On the incidence of degeneration, it seems still difficult to draw a conclusion. Clarke et al. [8] retrospectively analyzed 303 patients who underwent surgery for single cervical segment, and were followed up for 7.1 years on average, 15 of which had ASD with an annual risk rate of 6.4/1000 as shown by Kaplan - Meier survival curve, and 9 of which required surgery with a risk rate of 3.8/1000, an annual progression rate of 0.7%, and a 10-year progression rate of 6.7%. Fusion degeneration may occur in the adjacent segment above and below the plane of the adjacent segment, and both types and incidence rates may be different. Kulkarni et al. [9] reported 44 patients with cervical myelopathy underwent subtotal resection of vertebral body at C1-2 levels and were followed up for 17.5 months on average to assess the degree of

dural sac compression, intervertebral disc height, and sagittal diameter of vertebral canal in adjacent segment and distal segment by MRI, 33 (75%) of which had new and different degrees of dural sac compression in adjacent segments, including six severe cases, 7 and 9 of which had mild and moderate dural sac compression in distal segment respectively, and 11, 10 and 12 of which had degeneration in adjacent upper segment, lower segment and two segments respectively, and also found that the vertebral canal diameter of upper adjacent segment was reduced by 0.9 mm on average. Whether natural degeneration or fusion is the dominant factor in the occurrence of ASD has been the hot academic issues and the academic topic in debate in recent years [10]. Ishihara et al. [11] followed up 112 patients with anterior cervical fusion, 19 of which had ASD with an incidence rate of 19%, and found that if preoperative myelography or MRI showed spinal degeneration, the postoperative incidence would be higher. ASD caused by spinal fusion is still controversial. Etebar [12] reported 25 patients with an average follow-up of 44.8 months, and considered the incidence rate of adjacent segment degeneration was relatively low, only 3.9%. Ragab et al. [6] suggested in their studies that the change in adjacent upper and lower segment after bone graft and plate fixation showed no significant difference, and intradiscal pressure difference was < 30% in all directions and not statistically significant, Therefore it was considered that the anterior cervical fusion and fixation had no significant effect on the intervertebral disc pressure and movement of adjacent segment, and the clinically observed ASD was very likely to be the natural progression of vertebral degeneration.

Cervical total disc replacement

In recent years, cervical total disc replacement (TDR) has been performed extensively, Theoretically, TDR retains the segmental movement, reduces the stress of adjacent segments, and therefore significantly reduces the incidence of ASD. But the follow-up results after TDR seem to be unsatisfactory. Nunley et al. [13] followed up TDR patients for 2-4 years, and thought the risk of adjacent segment degeneration was same after ACDF as TDR. Park et al. [7] reported 22 patients with disc replacement and 21 patients with inter-body fusion had X-ray examination before operation and 5 years after operation. CT and MRI were used to determine the probability of ASD. It was found the incidence of ASD was similar (about 45%) in both groups of patients. These results indicated that the occurrence of ASD is a natural progression of the disease rather than an inter-body fusion. But some one also put forward different views. Yin et al. [14] analyzed the recent literatures and concluded that compared with ACDF, TDR did not reduce the incidence of ASD at 5 years after surgery, but the results after years remained unclear. And Hou et al. [15] reported the average 22-month follow-up observation with ASD incidence after ACDF higher than after TDR. Rosenthal et al. [16] considered similar incidence of adjacent segment degeneration after ACDF and TDR was caused by too short follow-up period, and if the follow-up period was 10 years or above, the incidence of adjacent segment degeneration after ACDF would significantly increase.

Effect of ACDF on adjacent segments in rabbits

Current clinical observations are retrospective, and lack of prospective results. Cadaver sample study can simulate a fixed pattern, but cannot reproduce fusion, which is not convincing. Animal experiment is a practical choice. Currently, successful fixation and fusion is mostly performed on the thoracolumbar part in the animal models [17-22]. Cervical spine models mostly come from large animals [23-26]. Because perioperative management of large animals is complex, endotracheal intubation and monitoring may be required. Due to limited space and funding, it is inconvenient to raise a large number of large animals for research. Therefore, the sample size of large animals is not enough to demonstrate the issue. Small animals are easy to raise and affordable, from which large number of samples could be obtained, but whose spine, especially cervical spine is too small to fix and fuse. Thus, successful models with cervical fixation and fusion are rare. We found that the number of activities of rabbit's cervical spine is much more than that of thoracolumbar part. When reared in the cages, most of the rabbits are in the supine or sitting position. Their cervical spine is in the vertical position, and can better reflect the human spine load than thoracolumbar part. Fixation and fusion should be performed on the

cervical spine of models. Compared with cattle, sheep and dogs, rabbits should not be raised in too greater area, and can be reared in great number so that enough samples can be obtained in an economical and convenient way. The cervical spine of rats is too small to have anterior fixation and fusion, and also difficult to observe by X-ray. In this study, it was found that cervical spine surgery in rabbits is fast and minimally invasive, brings little interference to animals, does not require endotracheal intubation and monitoring, and has simple and convenient perioperative management and high survival rate, all of which has provided a strong guarantee for experimental success. Therefore, this study used New Zealand white rabbits, and achieved success.

As seen from the immunohistochemical statistical results of this study, the difference was not statistically significant in the control group between 3 months and 6 months as well as between 6 months and 9 months, that is, the impact of 3-month aging would not cause the difference. The difference was statistically significant in the experimental groups between 3 months and 6 months as well as between 6 months and 9 months. The difference was statistically significant in 6 months and 9 months between the experimental groups and the control group. Therefore, we believed that anterior fusion and internal fixation in this experiment caused and accelerated degeneration of adjacent segments of intervertebral disc in rabbits. The observations of the effect of single segment fusion at different levels on adjacent segments of intervertebral disc showed: after fusion at the C3-4, C4-5 and C5-6 levels, degeneration occurred in adjacent upper and lower segments; after fusion at the C3-4 and C4-5 levels, the difference was not statistically significant between upper segment and lower segment; after fusion at the C5-6 levels, the difference was statistically significant between upper segment and lower segment, and degeneration was greater in the lower segment than in the upper segment. Schwab et al. [27] tested seven cervical specimens (C2-T1) from fresh cadavers, and observed the effect of single segment fusion at different levels on adjacent segment. The results showed that motion compensation of flexion and extension after spinal fusion occurred in adjacent segments, motion compensation at C3-4 and C4-5 levels occurred in upper adjacent segment, motion compensation at C5-6 and C6-7, levels occurred in upper and lower adjacent segments, but more obviously in the lower segment. Rao et al. [28] carried out studies on cervical specimens from seven fresh adult cadavers, and reported that flexion and extension after fusion and fixation at C5-6 levels could increase by 60% in the upper segment (C4-5) and by 15% in the lower segment (C6-7), and lateral flexion could increase by 51% in the upper segment and 16% in the lower segment, and axial rotational movement could increase by 25% in the upper segment and 200% in the lower segment. This may be one of the reasons why degeneration is severer in the lower segment than in the upper segment after C5-6 fusion in this experiment.

Conclusion

At present, the definite mechanism of ASD is unclear. After spinal fusion, the instant retroposition of rotation center of adjacent upper and lower segments of the vertebral body, the stress concentration of the small joints, the load increases, and repeated overload stress may be the reasons for degeneration of adjacent segments. In addition, the factor of ASD formation may also include the use of internal fixation, the number of fusion segments, fusion approach and location, abnormal physiological curvature of the spine, adjacent disc status, preoperative disease type, etc., which should be further investigated.

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Disclosure of conflict of interest

None.

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