ADHESION BARRIER GEL ANTIADGEZIN FOR DEGENERATIVE LUMBAR SPINE DISEASE*

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Objective. To assess the effectiveness of the application of adhesion barrier gel Antiadgezin to prevent the development of cicatricial adhesive process and its complications in the spinal canal after decompression surgery for degenerative disease in the lumbar spine.
Material and Methods. An open-label comparative randomized prospective clinical trial was conducted. The study involved 30 patients with degenerative lumbar spine disease who underwent decompression surgery. Patients were divided into two groups: in Group 1, gel Antiadgesin was injected during the spinal canal decompression, and in Group 2, the saline solution was injected. The severity of adhesive process was assessed according to MRI findings, and the severity of the pain syndrome and the degree of vital activity limitation were assessed by VAS and the Oswestry questionnaire in 2 weeks, 2 months and 1 year after surgery.
Results. Application of gel Antiadgesin allows reducing the probability of cicatricial process development in the spinal canal up to 35 % in comparison with the control group. The intensity of the cicatricial adhesive process development decreases by more than 3 times with the application of gel Antiadgesin. Reduction of pain syndrome according to VAS and restoration of physical activity are significantly more pronounced during the first weeks in Group 1. Infectious complications or allergic reactions in the study groups were not noted.
Conclusion. The use of adhesive barrier gel Antiadgesin during surgery reduces the likelihood of cicatricial adhesive process development in the spinal canal, which allows decreasing pain intensity and preventing disability in the postoperative period.
Key Words: gel Antiadgesin, adhesion, adhesion barrier, degenerative diseases of the spine, spinal canal decompression.

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One of the reasons for unsatisfactory functional outcomes of treatment and decline in the quality of life of patients operated on the lumbosacral spine is the development of persistent chronic pain syndrome in the lower back and/or legs in the postoperative period, which is referred to as Failed Back Surgery Syndrome (FBSS) [5, 17, 30, 33, 35]. The incidence of this complication ranges from 5 to 75 % [35]. In such cases, the alleged morphological substrate of the pain is often not diagnosed. The persisting vertebrogenic pain in the postoperative period can be attributed to many causes, most commonly to the formation of cicatricial adhesions in the epidural space [3, 12]. Neural structures can be affected both directly (compression by the scar tissue) and indirectly: compression of the veins in the epidural space leads to their expansion, which, in turn, causes compression of the nervous tissue [6, 26]. Persistence of the pain syndrome in the back or legs after discectomy or laminectomy often leads to disability or chronic dependence on analgesics. Typically, symptoms associated with epidural fibrosis appear several weeks after the surgery, after a period of decrease in pain syndrome [1, 20].

Due to the high incidence of this complication, researches have been actively looking for approaches to prevent the development of epidural fibrosis over the past decades. One of the most common solutions to the problem is transplantation of autologous adipose tissue into the epidural space. The idea behind this technique is to restore physiological barrier between the dural sac and the surrounding tissues. However, numerous studies have demonstrated that transplanted adipose tissue is also prone to fibrotic degeneration and does not reduce the risk of pain syndrome in the postoperative period. The results of most of this kind of studies did not reveal statistically significant differences in comparison with control groups and showed no signs of decrease in the volume of the developing scar tissue in the epidural space [2, 7, 12, 13].

During the last decade, the possibility of minimizing the activity of fibroblasts in the area of surgical intervention through exposure to low doses of radiation has been investigated [18, 31]. This variant of radiotherapy in the postoperative period is aimed at reducing the proliferative capacity of connective tissue, which, in theory, should significantly limit the formation of cicatricial adhesions in the epidural space. Even though the results of these studies have demonstrated relative effectiveness of the technique, its implementation is associated with limited availability and obvious risks.

*Advertorial.

Radiation exposure can adversely affect the process of restoration of the surrounding tissues, which significantly slows down the postoperative recovery.

Currently, there are ongoing preclinical studies using such chemotherapeutic drugs as "Tacrolimus", "Mitomycin C" and "Daunorubicin", which inhibit the proliferative activity of fibroblasts. These drugs affect various molecular mechanisms involved in the formation of fibrous tissue, in particular, stages of molecular cascades leading to the activation of apoptosis in fibroblasts. However, the results of experimental studies are ambiguous, most of them are in the initial stages only and are mainly limited to *in vitro* experiments [24, 32, 34].

Liu et al. [25] suggested the use of biodegradable polymeric membranes conjugated with NSAIDs as a solution to the problem of formation of cicatricial adhesions in the epidural space after a surgery. This approach was based both on establishing a physical barrier and on pharmaceutical treatment aimed at prolonged arrest of the local inflammatory process. The use of this technique is currently limited to preclinical studies and requires further study.

At present, the most promising solution to the problem of the development of epidural fibrosis is the use of drugs that serve as a physical barrier for formation of cicatricial tissue in the epidural space. "Gelfoam", "Oxiplex", "Gore-tex", "Seprafilm", "Adcon-L" can be highlighted among such drugs [4, 8–10, 14–16, 19, 21–23, 27–29]. These preparations are released in gel form and are injected directly into the spinal canal after surgical interventions. The results of the studies demonstrated statistically significant decrease in prevalence of postoperative fibrotic changes in the epidural space without adverse effect on the healing of the surrounding tissues. Biophysical barrier drugs are available, do not cause an inflammatory reaction and are fully biocompatible. They are biodegradable but persist in the area of administration for several weeks, which aligns with the period of formation of scar tissue.

Therefore, gaining clinical experience of the use of adhesion barrier gel, which would be based on an assessment of its effectiveness and safety in surgeries on the lumbosacral spine, is relevant.

The aim of the study was to evaluate the anti-adhesion efficacy and safety of the hyaluronic acid-containing gel Antiadgezin in decompressive surgeries in patients with degenerative lesions of the lumbar spine.

Antiadgezin is an anti-adhesion gel, whose main active substances are sodium salt of hyaluronic acid and sodium carboxymethylcellulose (HA-CMC).

Antiadgezin is intended to prevent adhesion after any surgeries on organs and tissues which are associated with a risk of undesirable adhesion of the soft tissues: in abdominal surgery and pelvic surgery, after surgeries in the uterine cavity and bladder, in spinal surgery, after surgeries on anatomical structures of the nose and paranasal sinuses, in ophthalmic surgery, etc.

To assess the achievement of the study goal, the following objectives were formulated:

1) to evaluate the effectiveness of antiadhesive gel Antiadgezin in preventing the development of cicatricial adhesive process in the area of revision of the spinal canal in case of degenerative lesions of the lumbar spine by examining MRI data before the surgery, 2 months and one year after the surgery;

2) to assess the clinical features of the course of postoperative period in case of application of Antiadgezin gel and the dynamics of the preoperative pain syndrome according to the VAS, compared to the pain syndrome in the postoperative period immediately after the surgery, 2 weeks, 2 months and 1 year after the surgery.

3) to assess the extent of disability using the Oswestry questionnaire (before the surgery, 2 weeks, 2 months and 1 year after the surgery);

4) based on the results of post-op monitoring of patients, to assess the safety of the anti-adhesion gel Antiadgezin during decompression interventions on the spinal canal (the incidence of allergic reactions, the incidence of infectious and inflammatory complications, abnormalities in complete blood count, the incidence of development of other undesirable phenomena).

Material and Methods

The study involved 30 patients with osteochondrosis of the lumbar spine, aged 18–60 years, who required decompressive surgery using metal fixation or without it. The patients were divided in two groups. The first (study) group consisted of 20 people who received injections of Antiadgezin gel immediately after the completion of the revision and decompression stage of the spinal canal surgery and after establishing adequate hemostasis between the wall of the spinal canal and the dural sac. The second (control) group consisted of 10 patients who received several milliliters of 0.9 % saline instead of Antiadgezin in the area of the intervention after the revision of the spinal canal.

Patients with individual intolerance or hypersensitivity reaction to hyaluronic acid, carboxymethylcellulose and their salts (based on their medical history), with obvious infection or contamination in the area of the surgery field, with allergic and autoimmune systemic diseases, immune disorders and with doubtful hemostasis were excluded from the study.

Simultaneous use of other antiadhesion agents during the surgery was excluded.

The severity of the adhesive process was assessed by MRI, according to the degree of dissemination of cicatricial fibrous tissue in the spinal canal. Five consecutive images at the level of the examined intervertebral space involving the lower 1/3 of the overlying vertebra, the disc (intervertebral space), and the upper 1/3 of the underlying vertebra (Fig. 1) were used for the calculations.

Each image was divided into 4 quadrants (a, b, c, d), and each quadrant in five images was used to evaluate the severity of the cicatricial process in the spinal canal in points (Table 1).

After summing up the points in each case, the sum was divided by 20 (the number of quadrants in five images) to obtain the average number of points

corresponding to the adhesive process in the spinal canal in the region of interest.

The severity of the pain syndrome in the lower back and legs was recorded using subjective assessment of the patient by VAS 2 weeks, 2 months and 1 year after the surgery. The extent of the vital activity limitation was assessed based on the results of the Oswestry questionnaire 2 weeks, 2 months and 1 year after the surgery. The dynamics of changes in the complete blood count before the surgery, after the surgery and 2 weeks after the surgery was recorded to identify infectious and allergic complications.

"SPSS Statistics 22" software and the Wilcoxon test were used for statistical processing of the data obtained.

Results and Discussion

According to the literature [4, 11, 14, 25], the use of anti-adhesive barriers can reduce the incidence of epidural fibrosis in the postoperative period, reduce the severity of the pain syndrome and improve the patients' quality of life. Compared to membranes, gel forms of the anti-adhesive barriers are currently preferrable, since they allow complete coverage of all the desired anatomical surfaces in a surgery wound and have adhesive properties and modified congruence.

Antiadgezin gel has been used in many areas of surgery (otorhinolaryngology, urology, obstetrics and gynecology, etc.) over 10 years. For example, according to a prospective randomized study conducted in South Korea's leading medical centers, the use of Antiadgezin gel in the area of spinal nerve roots can result in two-fold reduction in the development of cicatricial adhesion process after laminectomy in degenerative-dystrophic diseases of the lumbosacral spine (as assessed by MRI data). It was shown that 6 weeks after the surgery, patients who received Antiadgezin treatment were more satisfied with treatment than patients in the control group [14].

In our study, the main measure of the effect of Antiadgezin activity in the spinal canal was the assessment of the severity of the cicatricial adhesive process based on MRI data (Table 2). Tomograms were evaluated jointly with a leading researcher of the Department of X-ray Diagnostics. The number of points was calculated according to the scheme presented above. The severity of the cicatricial adhesive process of more than 1 point was not reported in any of the groups.

Based on the results of the analysis, there were statistically significant differences between groups ($p < 0.05$). An increase in the cicatricial adhesive process was reported in both control and study groups two months after the surgery, however, in the study group, a total of 7 (35 %) out of 20 patients reported an increase compared to 9 (90 %) out of 10 in the control group. A total of 26 out of 30 patients were examined one year after the surgery, and no statistically significant increase in the scar process was observed in both groups.

Therefore, the use of Antiadgezin gel allowed reducing the likelihood of development of the cicatricial adhesive process in the spinal canal up to 35 % in comparison with the control group. Dynamics of cicatricial adhesive growth in 2 months of follow-up in the study group were on average +4 % of the area of the spinal canal lumen compared to the average +13 % in the control group, which indicates a decrease in intensity of development of the cicatricial adhesive process by more than three times if Antiadgezin gel is used during the surgery (Fig. 2, 3).

The assessment of pain in the lower back by VAS (Table 3) showed more pronounced reduction in pain after 2 weeks with the use of Antiadgezin in comparison with the control group. There was a significant ($p < 0.05$) reduction in pain in both groups after 2 months. There was no statistically significant changes in dynamics in the distant period.

The assessment of the pain syndrome in the legs using the VAS (Table 4) revealed that pain syndrome significantly decreased in both groups ($p < 0.05$) both 2 weeks and 2 months after surgery, with a minor but statistically significant increase in the pain syndrome in the long-term period.

Comparison of the values of the Oswestry index (Table 5) 2 weeks after the surgery confirmed faster recovery of vital activity when using the Antiadgezin gel. Two weeks after the surgery, minor increase in the degree of disability was registered in the control group (from 45.4 to 48.2 %), whereas the group which received Antiadgezin gel demonstrated faster recovery of vital activity (decrease in the Oswestry index from 53.8 to 37.0 %). Significant positive dynamics of the functional state of patients was observed 2 months after the surgery compared to preoperative level both in the study (from 53.8 to 24.7 %, $p < 0.001$), and in the control (from 45.4 to 25.2 %, $p < 0.001$) groups. There were no statistically significant differences between the groups in the functional state according to the Oswestry scale two months and 1 year after the surgery. One year after the surgery, there was no worsening of the average indicators of the Oswestry index in all patients ($p > 0.05$).

The comparison of the results of the Antiadgezin gel application in patients who were stabilized with a metal fixation ($n = 13$) and patients without stabilization ($n = 7$) showed that there were no statistically significant differences in the early postoperative period and 2 months after the surgery, however, one year after the surgery, the degree of pain reduction and quality of life indicators were significantly better among patients who underwent instrumental fixation of the area of surgical intervention (Table 6).

There were no infectious complications or allergic reactions, or other undesirable reactions associated with the use of Antiadgezin in the study. The absence of infectious and allergic complications was confirmed by the complete blood count performed before and after the surgery (Table 7).

Significant differences were revealed between levels of hemoglobin, hematocrit, number of erythrocytes, platelets and ESR before the surgery and at the second week after the surgery in both groups. Based on the results of the Wilcoxon test, the following indicators changed significantly in the group of patients who received Antiadgezin: decrease in: concentration of hemoglobin, hematocrit, red blood cells; increase

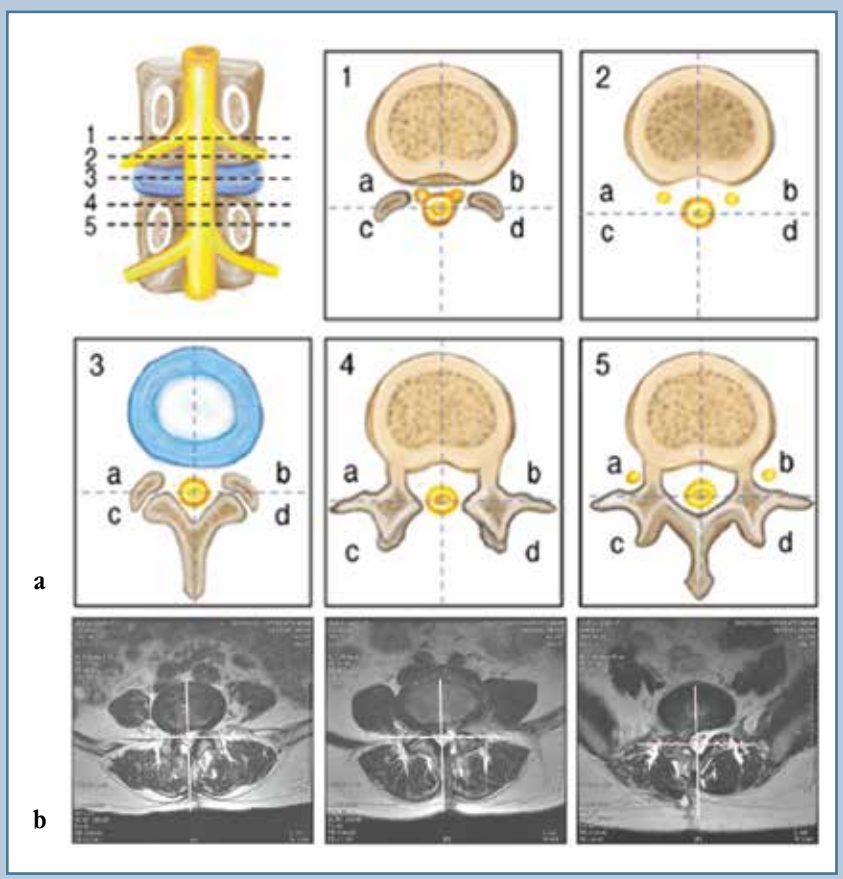

Fig. 1
Evaluation of the severity of cicatricial adhesive process according to MRI: **a** – scheme; **b** – division of axial sections of MRI into quadrants

Table 1
Assessment of severity of the cicatricial adhesive process

The severity of the cicatricial adhesive process, points	Description
0	There is no cicatricial and fibrous tissue in the spinal canal
1	Cicatricial and fibrous tissue fills 0—25 % of the quadrants
2	Cicatricial and fibrous tissue fills 26—50 % of the quadrants
3	Cicatricial and fibrous tissue fills 51—75 % of the quadrants
4	Cicatricial and fibrous tissue fills more than 75 % of the quadrants

in: concentration of platelets and ESR ($p < 0.05$). In the control group: decrease in: concentration of hemoglobin, hematocrit, red blood cells; increase in: concentration of leukocytes, percentage of stab neutrophils and ESR ($p < 0.05$). The dynamics of decrease in concentration of hemoglobin, hematocrit and erythrocytes was similar in both groups. In the control group at the second week after the surgery, there were signs of an inflammatory reaction according to blood indices: an increase in the average parameters of leukocytosis to 10.25 x 109/L, ESR - to 31.6 mm/h, whereas in the Antiadgezin group these values were significantly lower (7.72 x 109/L, ESR up to 24.15 mm/h).

As a proof that Antiadgezin has barrier functions, we provide the following clinical example.

Patient A., 52 years old, with osteochondrosis of the lumbosacral spine, herniated L5-S1 disc, lumboschialgia on the right. At admission, she complained of severe back pain (up to 9 points according to VAS), with irradiation to the lower left limb down to the foot on the back surface (up to 7 points according to VAS). She underwent transpedicular fixation at the L5–S1 level, revision, decompression of neural structures at the L5–S1 level and received Antiadgezin injection into the spinal canal in the area of decompression.

Two weeks after the surgery, the pain syndrome decreased to 5 points in the lumbar region and left lower limb. After 2 months these indicators decreased to 3 points. Limitation of vital activity according to Oswestry was 52% before the surgery and 26% at 2 months after the surgery. According to laboratory data, there were no allergic reactions or infectious process. The MRI data before and after the surgery are shown in Fig. 4.

Seven months after the surgery, the patient started to notice an increase in the pain syndrome above the level of instrumentation and disruption of the sagittal balance. The examination revealed proximal junctional kyphosis. A revision surgery was performed with the extension of the instrumentation. During the surgery, in order to study the effectiveness of Antiadgezin, it was decided to conduct an audit at the level of the previous surgical intervention (L5–S1), where the gel was used. During the revision, the entrance to the spinal canal was closed with rough scar tissue, however, in the area of the dural sac and its attachment to the canal walls, soft adhesions were observed, which made it possible to easily separate the dural sac from the surrounding scar tissue and the canal walls (Figure 5). Based on the intraoperative picture, it can be concluded that the barrier functions of the Anti-

Table 2
Patient distribution by severity of cicatricial adhesive process according to MRI, n

Degree of severity	Before the surgery		2 months after the surgery		1 year after the surgery	
	Study group	Control group	Study group	Control group	Study group	Control group
0	13	10	11	1	9	1
1	7	–	9	9	7	7
2	–	–	–	–	1	1
3	–	–	–	–	–	–
4	–	–	–	–	–	–

adgezin gel effectively prevent the development of rough fibrous-adhesive process in the spinal canal in decompressive interventions.

Conclusions

1. The use of adhesive barrier gel Antiadgezin during the surgery allows to reduce the likelihood of development of cicatricial process in the spinal canal up to 35% and preserves the area of the lumen of the spinal canal by more than 3 times (in the experimental group, on the average, +4 % of the area of the lumen of the spinal canal, in the control +13 %).

2. The assessment of pain in the lower back according to VAS showed more pronounced decrease in the lower back pain

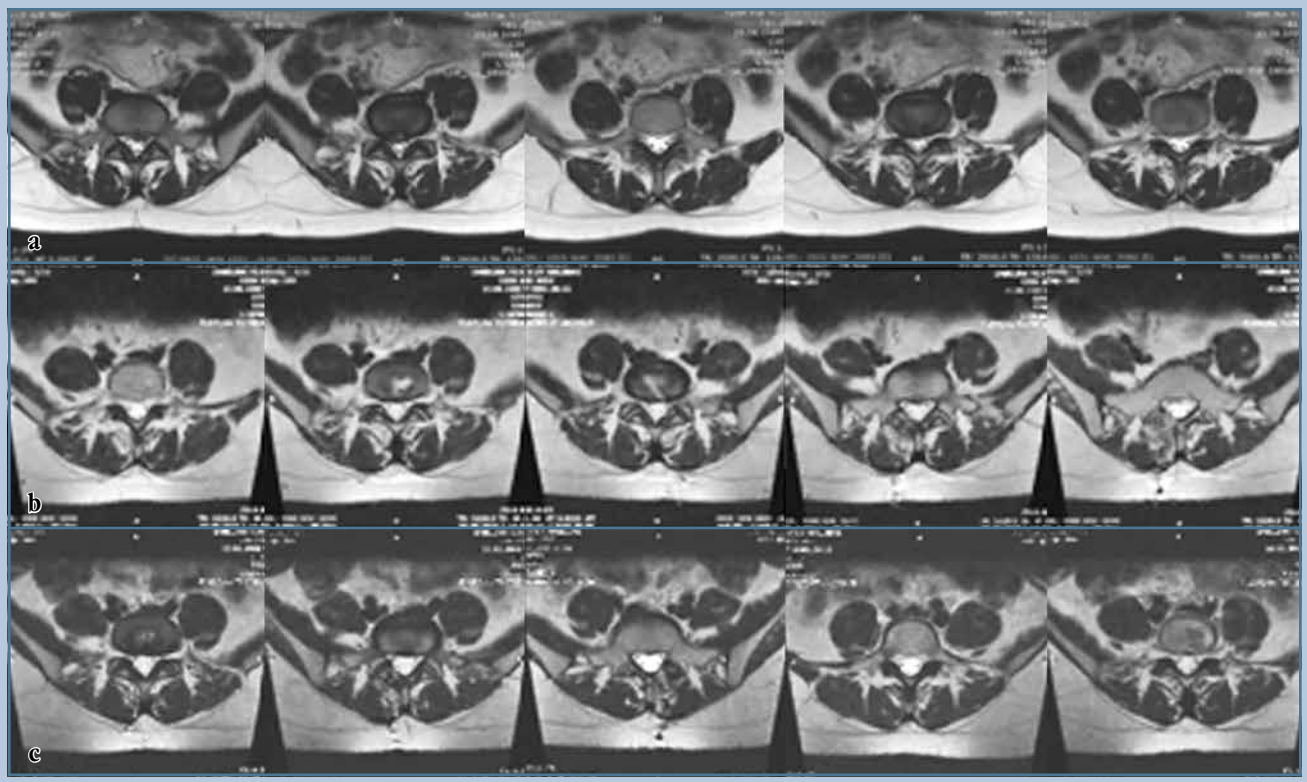

Fig. 2
MRI of patient A., 26 years old (study group), with herniated L5–S1 disc; operation in the volume of interlaminectomy, removal of herniated disc; application of Antiadgezin gel into the area of the dural sac and the walls of the spinal canal; severity of cicatricial process in quadrants at the level of surgical intervention before and after surgery 0 points: **a** – axial sections of the L5–S1 level before the operation; **b** – 2 months after the surgery; **c** – 1 year after the surgery

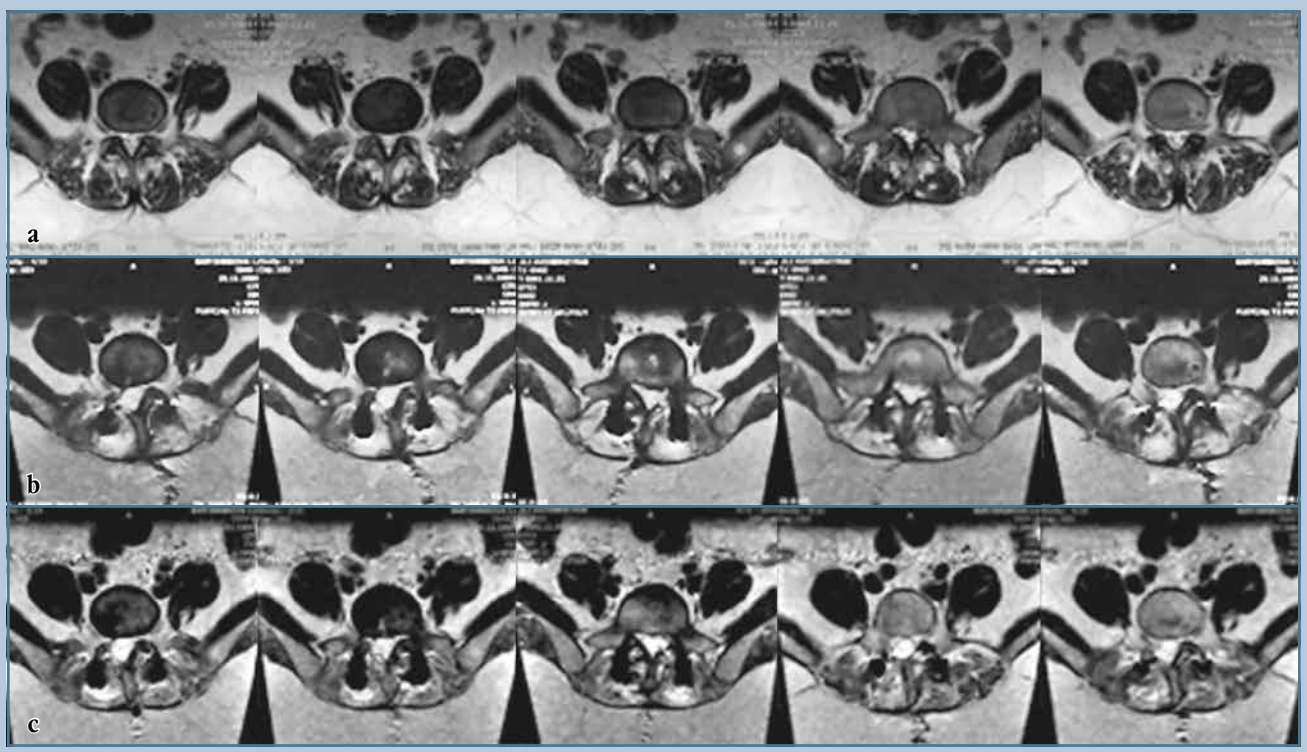

Fig. 3
MRI of the patient B., 46 years (control group), with osteochondrosis of the lumbar spine, Grade 1 spondylolisthesis at the level of L4, stenosis of the spinal canal at the level of L4–S1; surgery in the volume of transpedicular fixation at the level of L4–S1, interlaminectomy L4–L5–S1 on both sides, decompression of neural structures; saline solution was introduced into the area of the dural sac and the walls of the spinal canal; degree of severity of the cicatricial adhesive process before the surgery – 0 points, after the surgery – 0.15 points: **a** – axial sections of L5–S1 before the operation; **b** – after the surgery; **c** – 1 year after the surgery

Table 3
The severity of the pain syndrome in the lower back (VAS), points

Period	Group	
	Study	Control
Before the surgery	5.46 ± 3.48	6.41 ± 2.95
After 2 weeks	3.25 ± 2.17	5.15 ± 3.09
After 2 months	2.86 ± 1.26	3.13 ± 1.63
After 1 year	3.17 ± 1.84	2.93 ± 1.75

Table 4
The severity of pain syndrome in the legs (VAS), points

Period	Group	
	Study	Control
Before the surgery	6.22 ± 3.43	7.08 ± 4.08
After 2 weeks	3.17 ± 1.67	3.40 ± 1.82
After 2 months	1.79 ± 0.99	1.82 ± 1.27
After 1 year	2.21 ± 1.72	2.43 ± 1.94

in 2 weeks in the main group compared to the control group. Comparison of the values of the Oswestry index 2 weeks after the surgery also confirmed faster recovery of vital activity when applying the Antiadgezin gel. There were no statistically significant differences between the groups in the functional state based on the VAS and Oswestry questionnaire data 2 months and 1 year after the surgery.

3. The use of adhesive barrier Antiadgezin gel in surgical interventions on the spine is safe for patients, which is confirmed by the absence of allergic reactions or inflammatory complications in patients in our study according to laboratory tests before and after the surgery.

4. Comparison of the effectiveness of Antiadgezin gel in patients with and without instrumental fixation showed that stabilization provides better quality

Table 5

Degree of limitation in the patients' lives based on the results of the Oswestry questionnaire, %

Period	Group	
	Study	Control
Before the surgery	53.75 ± 21.93	45.44 ±19.77
After 2 weeks	37.0 ± 11.84	48.23 ± 25.14
After 2 months	24.67 ± 12.49	25.23 ± 18.36
After 1 year	23.18 ± 10.18	24.42 ± 19.6

of life in the long-term period without significant differences during the first months after the surgery.

The study was sponsored. The authors declare no conflict of interest.

Table 6

Comparison of the results of application of Antiadgezin gel in patients with and without instrumental fixation

Parameters	Before the surgery	2 weeks after the surgery	2 months after the surgery	1 year after the surgery
Pain syndrome in lower back (VAS). points				
With instrumental fixation	5.39 ± 3.78	3.14 ± 1.94	2.78 ± 1.64	2.91 ± 2.73
Without instrumental fixation	5.91 ± 1.97	3.39 ± 1.25	3.05 ± 1.91	3.86 ±1.77
p	0.104	0.129	0.321	0.019
Pain syndrome in legs (VAS). points				
With instrumental fixation	6.60 ± 3.57	2.97 ± 2.30	1.71 ± 1.30	1.90 ± 2.30
Without instrumental fixation	6.14 ± 1.57	3.29 ± 2.56	1.89 ± 1.86	2.57 ± 2.50
p	0.655	0.223	0.576	0.034
Limitation of vital activity according to the Oswestry questionnaire. %				
With instrumental fixation	47.60 ± 13.29	38.29 ± 14.56	22.80 ± 9.33	19.00 ± 11.40
Without instrumental fixation	55.43 ± 22.91	36.03 ± 11.25	24.29 ± 13.13	31.07± 11.31
p	0.061	0.059	0.095	0.001

Table 7

Mean values of complete blood count in patients in the main and control groups

Parameter	Before the surgery		2 weeks after the surgery	
	Study group	Control group	Study group	Control group
Hemoglobin, g/l	138.30	142.10	121.95	117.20
Hematocrit, %	39.87	41.24	35.27	33.58
Erythrocytes x1012/L	4.66	4.79	4.14	3.91
Platelets x109/L	252.05	298.30	292.50	303.20
Leukocytes x109/L	7.02	7.14	7.72	10.25
Stab, %	4.50	3.80	4.80	6.70
Segmented, %	54.35	60.30	54.85	60.00
Eosinophils, %	2.20	1.20	2.90	1.60
Basophils, %	0.35	0.20	0.40	0.30
Lymphocytes, %	27.80	27.10	26.05	22.90
Monocytes, %	8.70	7.30	9.75	8.00
ESR, mm/h	11.55	12.20	24.15	31.60

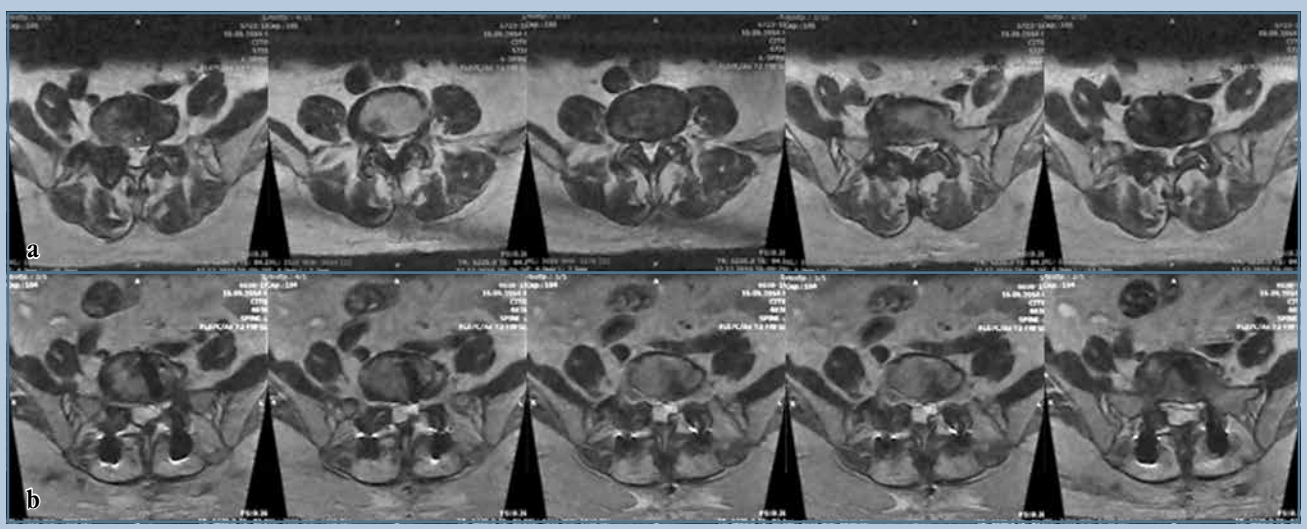

Fig. 4

Axial sections of MRI of the patient A., 52 years, before the surgery **(a)** and 2 months after the surgery **(b)**: the severity of the cicatricial adhesive process before the surgery – 0 points, after the surgery 0.04 points

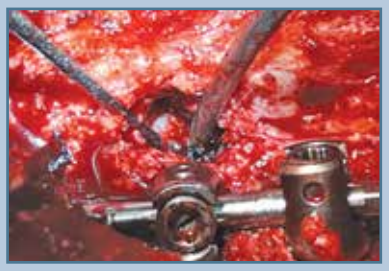

Fig. 5
Intraoperative photo of patient A., 52 years old: revision of the spinal canal at the level of the earlier (6 months) decompressive intervention; there are no signs of a pronounced fibrous adhesive process in the spinal canal

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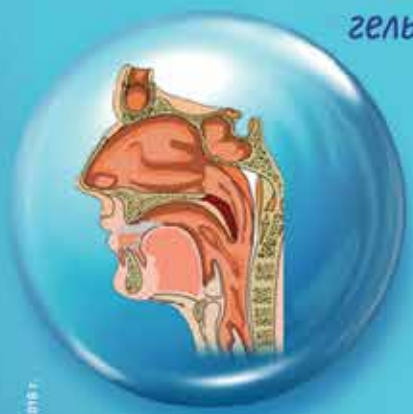

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