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Original Article

Correlations of O_3 therapeutic targets and imaging localization in lumbar intervertebral disc protrusion

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Abstract: Objective: This study aims to investigate correlations between the effects of O_3 target-injection treatment and imaging localization in lumbar intervertebral disc protrusion (LIDP). Methods: 164 LIDP patients were divided into 3 groups: group A, the protrusion located at level I-III, region 1-2, domain a-b; group B, the protrusion located at level I-III, region 1-2, domain c-d; group C: the protrusion located at level I-III, region 3-4, domain a-b. The patients were treated with LIDP O_3-target treatment + blocking therapy with epidural anti-inflammatory analgesic liquid. Results: Among the 164 LIDP patients, 95 patients (57.93%) exhibited the significant effectiveness after the treatment; 64 cases (39.02%) exhibited the effectiveness. The results of functional improvements revealed that 50 cases (53.76%) of sagittal plane and 54 cases of horizontal plane (55.67%) in the group A, 33 cases (35.48%) and 31 cases (31.96%) in the group C respectively were significantly better than those in the group B (10 cases, 10.75%; 12 cases, 12.37%) ($P < 0.05$). The visual analogue scale (VAS) scores 1 week and 1 month after the treatment in the three groups were significantly decreased than those before the treatment ($P < 0.05$). The intergroup comparison revealed that the A group (1 week 2.28 ± 0.85, 1 month 1.21 ± 0.27) and C (2.79 ± 0.98, 1.38 ± 0.55) were significantly better than the B group (3.92 ± 1.14, 2.53 ± 0.51) ($P < 0.05$). Conclusions: The O_3 target-injection treatment exhibited the best effects in treating the LIDP patients with the protrusion located at level I-III, region 1-2, domain a-b.

Keywords: Lumbar intervertebral disc protrusion, imaging localization, O_3 injection

Introduction

In recent years, the incidence of lumbocrural pain had obviously increased in China, and lumbar intervertebral disc protrusion (LIDP) was one of the main causes that resulted in the lumbocrural pain, in addition to drug therapies and surgical methods, the traditional conservative treatment in the department of Pain was the blocking treatment with epidural anti-inflammatory analgesic liquid [1], the curative effects had been confirmed, and it had been widely used and recognized in clinics. In recent years, such micro-invasive surgeries as O_3 [2], radio frequency [3], laser micro-invasive treatment [4], cervical discectomy [5] intervertebral disc mirror [6, 7] and intervertebral foramen mirror [8] had been widely used in clinics, not only obtained good curative effects, but also were safe and reliable, with less side effects. But how to forecast the curative effects of these methods, which were more analyzed from the patients' symptoms, signs, disease course, or general CT imaging findings. Hu proposed the regional localization method according to the intervertebral disc imaging performance [9], so we had more accurate understanding towards the shape, location and size of intervertebral disc, as well as its 3D relationships with the affected nerve roots, thus it had the instructive significance in clinic. From October 2009 to October 2013, according to this method, 164 LIDP patients were treated with the O_3-target treatment + blocking therapy with epidural anti-inflammatory analgesic liquid, and the treatment effects and CT imaging localization diagnosis [10] were retrospectively analyzed, aiming to provide the objective references for the effects of O_3 therapy and its correlations with intervertebral disc imaging localization in treating LIDP.

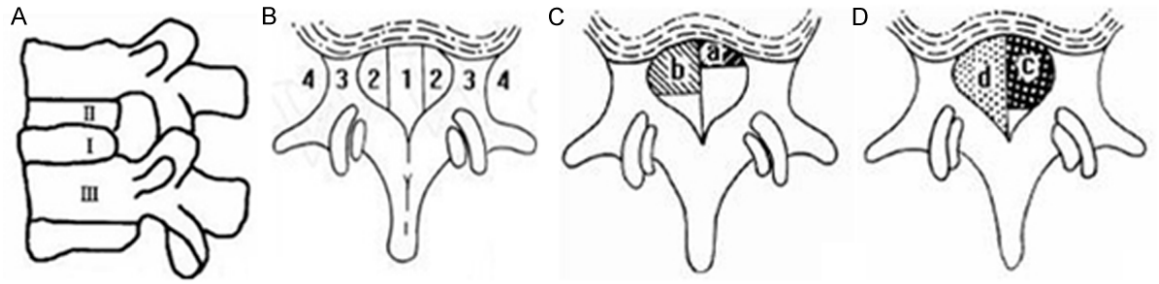

Figure 1. Schematic of lumbar disc herniation of CT three dimensional location.

Table 1. CT 3D localization of lumbar disc herniation patients

	CT regional localization	Cases (%)
Sagittal level	I	95 (57.93)
	I-II, I-III	69 (42.07)
Horizontal level	1-2,2	92 (56.10%)
	2-1-2, 2-3, 1-2-3	72 (43.90%)
Frontal level	a-b	111 (67.68%)
	c-d	53 (32.32%)

Materials and methods

General information

164 hospitalized LIDP patients were randomly selected, including 108 males and 56 females, aged 16 to 78 years old, with the average age as 46.33 ± 9.82 years old; the disease course was 7 days~3.5 years, with the average as 3.5 ± 2.64 months. The clinical manifestations were: 29 cases of simple backache (17.68%), 47 cases of single leg pain (28.66%), 98 cases of waist and leg pain (59.76%). The main signs were: 60 cases of deep tenderness beside the lumbosacral vertebra, which also radiated towards the lower limb (36.59%), 97 cases of positive straight leg-raising test (59.15%), 77 cases of thumb-extending muscle weakness (46.95%), 53 cases of thumb-flexing muscle weakness (32.32%), 29 cases of leg muscle atrophy (17.68%), 51 cases of hypalgesia at leg lateral foot dorsal skin (31.10%), 45 cases of Achilles tendon reflex weakness (27.44%), 28 cases of intermittent claudication (17.07%), 57 cases of different degrees of scoliosis (34.76%), and 3 cases of saddle area hypoesthesia and sphincter dysfunction (1.83%). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee. Written informed consent was obtained from all participants.

Imaging regional localization

All patients were confirmed as LIDP by computed tomography (CT) or magnetic resonance imaging (MRI). According to the division of regional localization method [9]: from the 3D point of view, the protruded intervertebral disc tissues had their own corresponding locations at the sagittal, horizontal and frontal positions of lumbar spinal motion segment (1) Sagittal position: divided into three levels: 1) the intervertebral disc level was named as level I; 2) the upper level of intervertebral disc, namely the inferior incisure vertebral plain of vertebral pedicle of upper intervertebral disc to the upper boundary of intervertebral disc, was named as level II; 3) the inferior layer of intervertebral disc was from the inferior boundary of intervertebral disc to the inferior incisure vertebral plain of vertebral pedicle of next vertebral body, also named as level III (**Figure 1A**). (2) Horizontal position: divided into 4 regions with the posterior vertebral boundary, namely, region 1, 2, 3 and 4. The region 1 and 2 were the inner boundary of bilateral vertebral pedicles, namely the prozone of vertebral canal, which was divided into three equal parts, the middle one third region was the region 1, and left and right one third regions were the left and right region 2; the region 3 was between the internal and external boundary of vertebral pedicle, namely within the boundaries of intervertebral foramens; the region 4 was outside the lateral vertebral pedicle (**Figure 1A**, **1B**). (3) Frontal position: from the posterior vertebral middle line to the frontal bone boundaries of vertebral processes, namely the bony vertebral sagittal diameter, and this sagittal diameter was divided into four equal parts, named domain a, b, c

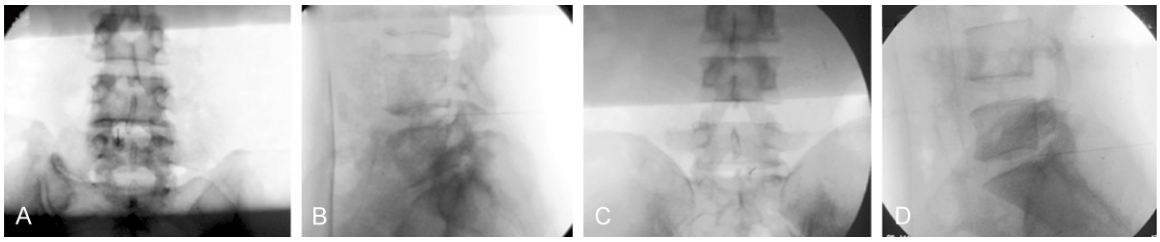

Figure 2. In the path of the needle. A: L4-5 facet joint medial edge approach (Anteroposterior); B: L4-5 facet joint medial edge approach (Lateral); C: L5-S1 facet joint medial edge approach (Anteroposterior); D: L4-5 facet joint medial edge approach (Lateral).

and d, respectively (**Figure 1C**, **1D**). The CT regional localization of the patients in this study was shown in **Table 1**.

Grouping

According to the situation of patient imaging data, divided the patients into three groups: A Group: The protruded intercalated disc located between level I-III, region 1-2, and domain a-b (n = 63); B group: the protruded intercalated disc located between level I-III, region 1-2, and domain c-d (n = 53); C group: the protruded intercalated disc located between level I-III, region 3-4, and domain a-b (48 cases).

Treatment

The patient was placed in the prone position for the fluoroscopic localization to determine the puncturing needle path. The L4-5 facet joint medial edge approach was adopted (**Figure 2**). The needling point was marked on the skin, followed by the regular disinfection and towel-spreading, as well as the local anesthesia with 1% lidocaine. Under the C-arm X-ray fluoroscopic guidance, the needle was proceeded until the LIDP target places, the needle tip should slightly deflect to the center when treating LIDP in region 1, and slightly deflect to the outside when treating LIDP in region 3-4, so that it could be closer to the target places. Used 10ml syringe to extract medical O_3 (with concentration as 45 to 50 μg/ml), and repeatedly bolus-injected at the LIDP places, with a total of 8-10 ml (**Figure 2**). Withdrew the needle tip to the inner stoma of intervertebral foramen, while without the cerebrospinal fluid and blood when withdrew, and then injected the sample quantity (1 ml) of 2% lidocaine, and watched for 15 minutes, if the patient had no signs of whole spinal anesthesia and anesthetic-entering-blood, injected the mixture of 1 ml Diprospan and 1.0 mg Mecobalamin (2 ml). Withdrew the needle after the surgery, dressed and banded the puncturing point. The patient should stay in bed for three days after the surgery, and rest for 2-4 weeks. CT review was carried out for patients 3-8 weeks after treatment (**Figure 3**).

Standards of therapeutic effect evaluation

The functional improvements were evaluated according to the improved low back pain scoring method of Japanese orthopaedic society [11], the pain was evaluated with the visual analogue scale (VAS) evaluation method. The low back pain scoring method adopted 4-level classification, and scored 0~3 points from light to heavy, respectively. The functional improvements were evaluated 1 month after the treatment. VAS scoring method was divided into 0 to 10 points, 0 point meant painless, 1~3 points meant the mild pain, 4~6 points meant the moderate pain, 7~9 points meant the severe pain, and 10 points meant the unbearable pain; the changes before the treatment, 1 week and 1 month after the treatment were evaluated.

Specific items: (1) subjective symptoms (6 points): 1) degrees of lumbocrural pain 0~3 points; 2) degrees of numbness 0 to 3 points. (2) objective symptoms (12 points): 1) degrees of lateral vertebral tenderness: none, light, medium and heavy. 2) Thumb flexion and extension muscle strength, divided into muscle strength level 5, muscle strength level 4~5, muscle strength level 3~4 and muscle strength below level 3. 3) the straight leg-raising and the strengthening test, divided into: > 70° negative strengthening test, > 45° positive strengthening test, > 30° positive strengthening test, < 30° positive strengthening test. 4) Radiation pain parts: no, the hip or thigh, calf and feet. (3)

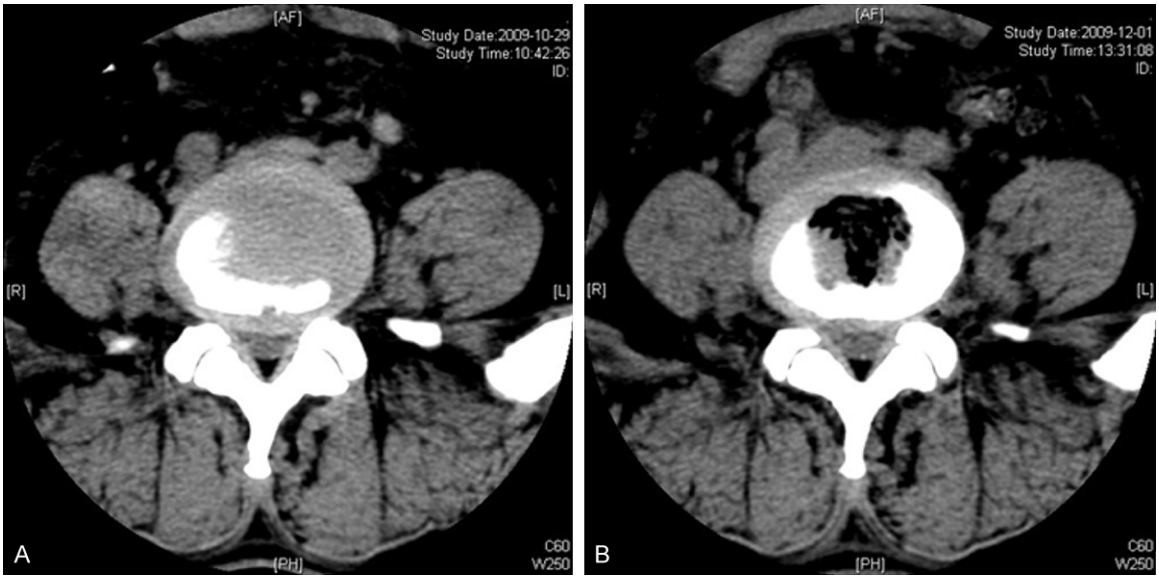

Figure 3. Image change before and after treatment. A: L4-5 before lumbar disc treatment (I, 1-2, a); B: 3w after treatment, herniation smaller at CT.

abilities of daily work and life (12 points): 1) the abilities of bending-waist and lifting-heavy objects were divided into: could normally bend waist, and carry more than 3 kg weight; could bend, but could not lift more than 3 kg weight; could not bend and could not lift more than 3 kg weight; serious obstacle in bending-waist and lifting-heavy objects. 2) walking distance or time was divided into: could walk 1000 m or more than 60 minutes; could walk 500 m or more than 30 minutes; could walk 100 m or more than 10 minutes; with walking difficulty. 3) daily bed-lying time was divided into < 10 h, 10~12 h, 13~16 h, > 16 h. 4) working abilities could be divided into: could do the original full-time job; could work, but occasionally needed rest; could work, but often needed rest; could not work.

The total score of this evaluation table was 30 points, and according to the classification of disease degrees, the patients with the total score < 10 points were classified as mild, with the total score as 11 to 20 points were classified as moderate, with the total score as 21~30 points were classified as serious.

Improvement rate: [(score before treatment - score after treatment) ÷ score before treatment] × 100.

Significantly effective: improvement rate > 60%; Effective: improvement rate from 30 to 60%; Invalid: improvement rate < 30%.

Statistical analysis

All the counting data were expressed as case numbers, and the measurement data were expressed as $\overline{x} \pm S$, and performed the statistical analysis with SPSS 13.0, the inner group comparison used the single factor analysis of variance and the paired t test, and the inter-group comparison used the double factor analysis of variance, with $P < 0.05$ considered as the significant difference.

Results

One month after treatment, among the 164 patients, 95 cases exhibited the significant effectiveness, accounting for 57.93%; 64 cases exhibited the effectiveness, accounting for 39.02%; and 5 cases were invalid, accounting for 3.05%.

The comparison of regional localization distribution among the 3 groups was shown in **Tables 2** and **3**. The data were analyzed according to the LIDP imaging localization method, and the regional distribution analysis of sagittal plane revealed that 97 cases exhibited the significant effectiveness, among which the A group had 50 cases (53.76%), and the C group had 33 cases (35.48%), significantly higher than the B group (10 cases, 10.75%). The regional distribution analysis of horizontal plane revealed that 93 cases exhibited the significant effectiveness,

Table 2. Lumbar disc partition and effect relationship between the Sagittal level Cases (%)

Effects	Cases	Group (%)		
		A	B	C
Significantly effective	97	54 (55.67)$^{\Delta}$	12 (12.37)*	31 (31.96)*,$^{\Delta}$
Effective	62	9 (14.52)	37 (59.68)*	16 (25.81)
Invalid	5	0	4 (80.00)*	1 (20.00)

*Compared with the A group, *P < 0.05, with the statistical significance. $^{\Delta}$compared with the B group, P < 0.05, exhibiting the statistical significance.

Table 3. Lumbar disc partition and effect relationship between the horizontal position Cases (%)

Effects	Cases	Group (%)		
		A	B	C
Significantly effective	93	50 (53.76)$^{\Delta}$	10 (10.75)*	33 (35.48)*,$^{\Delta}$
Effective	66	13 (19.70)	39 (59.09)*	14 (21.21)
Invalid	5	0	4 (80.00)*	1 (20.00)

*Compared with the A group, *P < 0.05, with the statistical significance. $^{\Delta}$Compared with the B group, P < 0.05, exhibiting the statistical significance.

Table 4. The VAS scores before and after treatment in each group ($\bar{x} \pm s$)

Group	Before treatment	1 week after treatment	1 month after treatment
A	6.23 ± 1.52	2.28 ± 0.85*	1.21 ± 0.27*
B	6.81 ± 1.85	3.92 ± 1.14*,$^{\Delta}$	2.53 ± 0.51*,$^{\Delta}$
C	6.95 ± 2.12	2.79 ± 0.98*	1.38 ± 0.55*

*Compared with those before treatment, *P < 0.05, exhibiting the statistical significance; $^{\Delta}$compared with the A group, P < 0.05, exhibiting the statistical significance.

among which the A group had 54 cases (55.67%), and the C group had 31 cases (31.96%), significantly higher than the B group (12 cases, 12.37%).

One week and one month after the treatment, the VAS scores of all the groups were significantly decreased when compared with those before the treatment, and the differences were statistically significant; the intergroup comparison revealed that the A (1 week 2.28 ± 0.85, 1 month 1.21 ± 0.27) and C (2.79 ± 0.98, 1.38 ± 0.55) group were also significantly better than the B group (3.92 ± 1.14, 2.53 ± 0.51), and the detailed results were shown in **Table 4**.

Discussion

LIDP was the common cause of such clinical symptoms as lumbocrural pain and numbness, the main mechanisms of LIDP-caused nerve root pain included the mechanical compressions, chemical inflammatory reactions and immune inflammatory reactions, these pathological changes might co-exist at the same time or one pathological change might be the main contradiction [12, 13]. Therefore, the treatment of LIDP should perform not only the disc decompression, but also the anti-inflammatory treatments around the nerve roots. Certain literatures reported that O_3 could not only achieve the purpose of decompression, but also obtain the anti-inflammatory effects when used in treating LIDP. The animal experiments and clinical treatments [14] showed that the principle of O_3-inuced decompression was because O_3 could oxidize the nucleus pulposus, thus making the nucleus pulposus dehydrated and shrinking; meanwhile, its anti-inflammatory approaches were analyzed as: (1) could induce the excessive expression of antioxidant enzymes, thereby eliminating inflammation, as well as the reactive oxygen species excessively expressed in other physiological and pathological processes; (2) could cause the tissue cells to produce NO and platelet-derived growth factor (PDGF), and promote the vasodilation in the lesion areas, increase the oxygen-supply in the lesion areas, thereby promoting the inflammation absorption; (3) could spur the generation of anti-inflammation cytokines, such as IL-10 and TGF-, etc., and inhibit the activities of NF-κB, inhibit the cells' expressing the inflammatory factors (such as IL-1, IL-2, IL-6 and TNF-, etc., [15, 16] and reduce the serum IgG, IgM in the LDH patients [17]. The inflammations around the nerve roots were mainly derived from two aspects, one was from the protrusion's nucleus pulposus tissues-secreted inflammatory cytokines, and the immune antigen-antibody complexes-caused inflammations, the other hand

was because the protrusion's nucleus pulposus tissues oppressed the dural sac, nerve root and their surrounding vessels, which led to the aseptic inflammations inside the disc and its surrounding areas [18, 19]. In addition to the injection of O_3 into the lesion spinal nucleus pulposus, it would be very important that whether O_3 could be injected into, or enter the nucleus pulposus, thus it could minimize the protrusion degrees of nucleus pulposus (or disc), and achieve the ideal effects of nerve root decompression, as well as the therapeutic effects towards the inner-disc aseptic inflammation; on the other hand, certain research reported that the combination of radio frequency target thermal coagulation and epidural nerve blocking was better than the single radio frequency therapy [20], we also adopted the method which withdrew the needle back to the intervertebral foramen, then injected Diprospan + mecobalamin, and achieved the purposes of alleviating and eliminating the inflammatory edema of dural sac, nerve root and surrounding vessels, as well as nerves nutrition and protection. So during the treatment, we adopted the target-puncturing injection method in order to achieve the treatment effects, and the statistical results proved the feasibilities and effectiveness of this method.

But what other pathological factors might affect the effects of LIDP treatment? When encountered these problems previously, we generally analyzed and judged the situations from the patients' symptoms, signs, disease courses or general CT imaging findings. Hu proposed the regional localization method which was based on the intervertebral disc imaging performance [9], so we had more accurate understanding towards the shape, location and size of intervertebral disc, as well as its 3D relationships with the affected nerve roots, certain literatures reported the curative effects of massage and epidural blocking in treating LIDP, and analyzed the correlations between them with this kind of classification method [21, 22], while the correlations between this localization method and O_3 target injection treatment were not reported. In this paper, the regional localization method was combined with different pathological changes of nerve roots to analyze its correlations with the O_3 treatment, and it was considered that the related factors included the degrees of compression and chemical immune inflammatory reactions of nerve roots. (1) The compression degree of nerve root LIDP lied in the region 1 and 2 of imaging horizontal level belonged to the central or para-central protrusion, and that in the region 3 belonged to the intervertebral foramen protrusion. As for LIDP with the same size, the lesions in the region 1 and 2 might exhibit lighter symptoms of nerve root compression, because there existed certain buffer in these regions, so the nerve root would not be directly oppressed, and most treatments would be effective, while when LIDP was in the region 3 and 4, the nerve roots would be squeezed within the pedicles that had the same sequences, which exhibited the most direct and serious compression and stimulation towards the nerve roots, so the symptoms and signs would be heavier. The regional localization of LIDP in the imaging frontal level would reveal the size and degree of LIDP. With this method, the spinal canal diameter was divided into four equal parts, each one quarter represented one level. The bigger protrusion, the heavier degree of dural and nerve root compression. Among the effectiveness group of this study, the cases of domain a and b were obviously higher than those of domain c-d, therefore, the O_3 treatment effects were poor towards the patients with LIDP in domain c-d, especially those accompanied with the compression symptoms in nerve roots or cauda equina, and they should be performed the micro-invasive intervertebral foramen mirror surgery or open surgery as early as possible. (2) The imaging sagittal layering and frontal regional localization towards the degrees of nerve root chemical immune inflammatory reactions could help us to understand the pathological types of LIDP whether it was the bulge type, the protrusion type, the emersion type or the free type. If LIDP was of level III domain c- or level II domain c-d, it belonged to the ablated-mallet or upwards-warping type of LIDP, the fibrous ring broke, and the nucleus pulpous contained the substances that could strongly cause inflammation and allergy, the protrusion or leakage could cause the severe chemical immune inflammatory reactions inside the spinal nerve roots, and the O_3 treatment would be difficult to completely eliminate this kind of protrusions. From the analysis results, we could conclude that 5 cases were invalid, among which the protrusion of 1 case was in level I-II, region 2, domain b, the protrusions of 3 cases were in

level I-III, region 1-2, domain b-c, and the other 1 case was in level II, region 2, domain b, while accompanied with severe degenerative intervertebral foramen stenosis. As for the patients with severe upwards-warping or drooping (protrusions at level II and III, region 1-2, domain b-d), the direct mechanical compression of nerve roots or accompanied with severe chemical immune inflammatory reactions would be the main pathological changes, considering the O_3 treatment might often have difficulty to change the above pathological changes, the intervertebral foramen mirror technology or surgery could be recommended. Most protrusions in level I, region 1-2, domain a-b were small, belonging to the inclusive protrusion that had the complete fiber rings, and the nerve root compression was indirect and lighter, the main pathological changes would be the low level chemical immune inflammatory reactions, thus the O_3 treatment + blocking of anti-inflammatory analgesic injection liquid could eliminate edema and inflammatory reactions, as well as improve the microcirculation, thus good effects could be obtained.

In summary, the imaging localization diagnosis of LIDP had obvious correlations with the curative effects of O_3 injection in treating LIDP, which could partially reflect the pathological changes of nerve roots, thus providing the objective basis for the efficacy prediction of O_3 injection in treating LIDP, at the same time, this regional localization method could also be used to provide the objective reference basis for predicting the curative effects of other LIDP treatment methods.

Disclosure of conflict of interest

None.

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