

Accurate location and minimally invasive treatment of lumbar lateral recess stenosis with combined SNRB and PTED Journal of International Medical Research 48(3) 1–11 © The Author(s) 2019 Article reuse guidelines: sagepub.com/journals-permissions DOI: 10.1177/0300060519884817 journals.sagepub.com/home/imr



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Abstract

Objective: To establish a management strategy for multi-segment lumbar lateral recess stenosis. **Methods:** A retrospective study was performed in patients in whom suspected responsible nerve roots underwent sequential selective nerve root block (SNRB). Based on pain remission rate after blocking, the contribution of nerve root compression to symptoms was classified as absolutely (\geq 70%) or relatively (30–70%) responsible or non-responsible (<30%). Conservative treatment was continued if visual analogue scale (VAS) at 3 days after blocking a single nerve root or VAS at 3 days after blocking multiple nerve roots was \geq 50%; otherwise, percutaneous transforaminal endoscopic discectomy (PTED) was performed. Pain and functional scores were evaluated on day 3, 6 months and 1 year after SNRB or PTED.

Results: Fifty-seven of 80 patients had a single absolutely responsible root, 20 had 2 responsible roots, and 3 had 3 responsible roots. Among them, 41, 10, and 1 patient underwent PTED, respectively. Both the PTED and conservative groups improved significantly in VAS remission rate and functional scores compared with admission. Moreover, the PTED group had a better VAS remission rate compared with the conservative group.

Conclusion: A combination of SNRB with PTED was effective for diagnosing and treating multisegment lumbar lateral recess stenosis.

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Keywords

Minimally invasive, multi-segment, lumbar lateral recess stenosis, diagnosis, treatment strategy, nerve root block

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Introduction

Multi-segment lumbar lateral recess stenosis is commonly observed in the clinical setting, especially in the elderly population. It is characterized by extensive degeneration of the lumbar spine with lateral recess stenosis on imaging, atypical symptoms, and usually an unclear diagnosis.¹ Multisegment open surgery and fixation were often performed to decompress the stenosis completely and to reestablish spinal stability. However, open surgical treatment is associated with several issues such as massive trauma, bleeding, and a high incidence of postoperative complications. Therefore, identifying the responsible segment and applying minimally invasive surgery would be expected to benefit a patient's prognosis. For this purpose, our goal was to apply selective nerve root block (SNRB) combined with percutaneous transforaminal endoscopic discectomy (PTED) to assist with the correct diagnosis and treatment of patients with multi-segment lumbar lateral recess stenosis.

Methods

Patient inclusion and exclusion criteria

This was a retrospective study analyzing patients who were treated in our department for lumbar lateral recess stenosis. Inclusion criteria were as follows: (1) unilateral lower limb symptoms with persistent radiating pain and a visual analogue scale $(VAS)^2$ score of ≥ 5 ; (2) at least 2 segments

of lumbar stenosis were supported by imaging; (3) the imaging data were consistent with the clinical symptoms; (4) although patients had combined motor and sensory deficits, we could not locate a specific responsible segment based on signs and imaging findings; and (5) failure of conservative treatment after at least 6 months.

Exclusion criteria were as follows: patients with (1) severe low back pain; (2) lumbar disc herniation; (3) lumbar instability and spondylolisthesis; (4) central lumbar spinal stenosis; (5) spinal tumors, tuberculosis, scoliosis, kyphosis, spondylolisthesis, instability, or pelvic and lower extremity joint diseases; (6) previous surgery; and (7) poor physical condition to tolerate surgery.

This study was approved by our local hospital ethics committee (the First Affiliated Hospital of Soochow University and the Affiliated Hospital of Medical School of Ningbo University) and patients provided informed consent regarding the publication of their data. This study was conducted in compliance with relevant Equator network guidelines.

Treatment strategy

Predicting the responsible nerve root. According to the patient's history, physical signs, radiographic examinations, and the clinical experiences of senior doctors, the potentially responsible nerve roots were proposed and ranked. After that, nerve root block was performed sequentially based on ranking until all responsible nerve roots were identified. In the event of a puncture or block failure, the operation was repeated on the following day.

Identifying the responsible nerve root and formulating treatment plan. Patients а returned to the ward after the most suspected responsible nerve root had been blocked. The VAS-2h (2 hours after blocking) score was evaluated to obtain the VAS remission rate. The formula⁴ of VAS remission rate, (VAS pre-blocking - VAS post-blocking)/VAS pre-blocking) $\times 100\%$, could also be expressed as "the remission of VAS score/VAS pre-blocking×100%". After blocking a suspected responsible nerve root, if the VAS-2h remission rate was \geq 70%, it was considered an absolutely responsible nerve root; if the VAS-2h remission rate was <30%, it was excluded as the responsible nerve root; if the VAS-2h remission rate was between 30% and 70%, it was considered a relatively responsible nerve root, and then it was necessary to continue to block the second most suspected nerve root in the ranking until the sum of the VAS-2h remission rate was >70%. In short, the diagnosis of multiple responsible nerve roots had to fulfill 2 conditions: 1) the VAS-2h remission rate should be between 30% and 70% after a single suspected nerve root block (relatively responsible nerve root); and 2) the sum of the VAS-_{2h} remission after blocking these relatively responsible nerve root block had to be $\geq 70\%$.

When patients with either a single absolutely responsible nerve root or multiple relatively responsible nerve roots were identified, we then observed the VAS-3d (3 days post-blocking) remission rate. If the VAS-_{3d} remission rate was still \geq 50%, it was considered a good blocking effect and patients continued to receive conservative treatment. If the VAS-3d remission rate was <50%, it indicated that the blocking result was minimal, and suggested that the nerve root(s) was (were) severely compressed, and single- or multi-segment PTED was performed (Figure 1). A typical case is presented in Figure 2.

SNRB technique. The patient was placed in the prone position, and the exit of the nerve root at the intervertebral foramen was targeted (the target would be the first sacral foramina if the first sacral nerve root was involved). With the aid of a C-arm X-ray machine, an 18G puncture needle was passed through the side of the lumbar vertebrae to the intervertebral foramen where the nerve root exited (close to the outer lower edge of the pedicle, but not entering the intervertebral foramen). If the nerve root was stimulated, the radiating pain along the nerve innervation area would be reproduced. Thus, the needle tip was slightly retracted, followed by an injection of 0.5 mL iohexol contrast agent. Fluoroscopy revealed the distribution of contrast agent along the nerve root. Subsequently, 0.5 mL of the blocking solution (0.25 mL of 1% lidocaine and 0.25 mL of betamethasone) was injected. If the contrast agent was not distributed along the nerve root after injection, then the position of the needle tip was adjusted until the nerve root was visualized, followed by injection of the blocking solution.

PTED technique. The patient was placed in the prone position with the abdomen uncompressed. After that, the lines, such as the spinous process line, iliac crest line, the line of the responsible level, and the safety line were marked on the body surface using a C-arm X-ray machine. The site and puncture pathway of the puncture needle were marked according to the surgical segment, target, and patient's habitat. After routine disinfection and draping, 0.5% lidocaine was administered for infiltrating anesthesia via an 18G needle. Under the guidance of a C-arm X-ray machine, the needle was punctured toward the target,



Figure 1. Minimally invasive diagnostic and therapeutic strategies for multi-segment lumbar lateral recess stenosis.

and the working channel was established through gradual expansion. The ventral part of superior articular process was first removed, and the intervertebral foramen and lateral recess were then enlarged using the trephine and microscopic abrasive drill. Furthermore, the thickened ligamentum flavum, the herniated intervertebral disc, or the nucleus pulposus in the intervertebral foramen were removed as required, followed by freeing of the impacted nerve root. Three mL of blocking agent (2 mL of 0.375% ropivacaine and 1 mL betamethasone) was injected around the nerve root, and then the working channel was removed, followed by closure of the incision. Twenty-four hours after surgery, the patients were allowed to get out of bed with waist support. On day 3 after surgery, the decompression of the lateral recess was evaluated by lumbar CT.

Clinical evaluation

For SNRB, the VAS of leg pain and the VAS remission rate were compared between pre-blocking and 2 hours after blocking the suspected responsible nerve root. After identification of the responsible nerve root, the VAS of leg pain and the VAS remission rates were compared between pre-blocking and 3 days after blocking the single absolutely responsible nerve root or multiple relatively responsible nerve roots.



Figure 2. Typical case: a 68-year-old male patient with pain in the right lower limb, accompanied by restricted walking for 3 years, had aggravated pain for 4 months. A: Lumbar MRI – right sagittal position; B: Lumbar MRI – L3/4 cross-section; C: Lumbar MRI – L4/5 cross-section showed lumbar 3/4, 4/5 right lateral recess stenosis; D: Intraoperative fluoroscopy of L4 nerve root block; E: Intraoperative fluoroscopy of PTED; G: Complete decompression of the right nerve root of L5 was seen; H: Lumbar CT – right sagittal position; I: Lumbar CT – L3/4 cross-section showed removal of most of the right superior articular processes of L4 and L5, and full decompression of the lateral recesses.

The clinical symptoms at admission, 3 days after blocking, and on day 3, 6 months and 1 year after PTED were evaluated. The assessment included VAS, lower back pain score standard index of the Japanese Orthopedic Association (JOA),⁴ and Oswestry Disability Index (ODI).⁵

Statistics

All statistical analyses were performed using SPSS 19.0 software (IBM Corp., Armonk, NY, USA). The data were expressed as means \pm standard deviation. The intergroup differences were analyzed by *t*-test. *P*-values <0.05 were considered to be statistically significant.

Results

Baseline data and methods

A total of 80 patients diagnosed with multisegment lumbar lateral recess stenosis in our department between August 2013 and August 2017 were selected according to the criteria mentioned above. We included 48 males and 32 females, aged 56-93 years old (average, 64.6 years) and with a 0.5-20-year (average, 7.8 years) duration of symptoms. The VAS score of the patients with sustained radiating leg pain at admission ranged from 5.0 to 8.6 points (average, 6.7 points). All patients showed a positive straight leg raise sign on the affected side, but were not positive for hypoesthesia and muscle weakness on the affected lower extremity. All patients underwent comprehensive radiographic examination, including lumbar X-ray, computed tomography (CT), and magnetic resonance imaging (MRI). CT showed ≥ 2 segments of facet joint degeneration and lateral recess diameter of $\leq 3 \text{ mm}$,⁶ which confirmed the diagnosis of multi-segment lumbar lateral recess stenosis. However, the specific responsible segment could not be determined by physical examination and radiographic studies.

| | l root (57 cases, 71%) | | | | 2 roots (20 cases, 25%) | | | 3 roots (3 cases, 4%) | | |
|----------------------|------------------------|----|----|----|-------------------------|-------|--------|-----------------------|-----------|--|
| Segment distribution | L3 | L4 | L5 | SI | L3,4 | L4, 5 | L5, SI | L3, 4, 5 | L4, 5, SI | |
| | I | 9 | 32 | 15 | 4 | П | 5 | 2 | 1 | |

 Table 1. Distribution of responsible nerve roots in 80 patients.

Table 2. Treatment plans based on VAS_{-3d} remission rate.

| Responsible nerve root types and cases | Conservative treatment (VAS_{-3d} remission rate \geq 50%) | PTED (VAS _{-3d} remission rate <50%) |
|---|--|---|
| l root, 57 | 16 (28%) | 41 (72%) |
| 2 roots, 20 | 10 (50%) | 10 (50%) |
| 3 roots, 3 | 2 (67%) | I (33%) |

VAS, visual analogue scale. PTED, percutaneous transforaminal endoscopic discectomy.

SNRB

Evaluation of VAS_{-2h} remission rate to determine the responsible nerve roots. All 80 patients underwent SNRB. According to the VAS_{-2h} remission rate, there were 57 patients (71%) with a single absolutely responsible nerve root, 20 cases (25%) had 2 relatively responsible nerve roots, and 3 cases (4%) had 3 corresponding responsible nerve roots. The specific responsible nerve root distribution is shown in Table 1.

Evaluation of VAS_{-3d} remission rate to determine the treatment plans (Table 2). Among the 57 cases of single absolutely responsible nerve roots, there were 16 cases (28%) with a VAS-3d remission rate >50% and they continued to be provided conservative treatment. The remaining 41 patients (72%)underwent single-segment PTED. Similarly, among the 20 cases with 2 relatively responsible nerve roots, 10 cases (50%) had a VAS_{-3d} remission rate \geq 50% and were continued to be provided conservative treatment. Among the 3 cases of 3 relatively responsible nerve roots, 2 cases (67%) had a VAS_{-3d} remission rate \geq 50% and were continued given conservative to be

treatment. All remaining patients underwent PTED of either 2 or 3 segments.

PTED

Fifty-two patients with a VAS_{3d} remission rate <50% underwent PTED to decompress the responsible lateral recess and the nerve roots. The average length and bleeding associated with surgery were as follows: the average time for a single segment was about 75 minutes, and the bleeding was about 5 mL; the average time for double segments was about 125 minutes, and the bleeding was about 10 mL; the average time for three segments was about 200 minutes, and the bleeding was about 20 mL.

No complications such as nerve root injury or dural rupture were observed during the operations, and no infections occurred postoperatively. Three days after the operation, lumbar CT showed that most of the hyperplastic superior articular processes were removed, and the lateral recesses were fully decompressed.

In addition, of the 28 patients who underwent conservative treatment, 3 patients developed symptom recurrence in the next year. The VAS remission rate at the time of recurrence was <50% relative

| Compared with the VAS of leg pain at admission | VAS remission rate | VAS remission rate | VAS remission rate |
|--|---|---|---|
| | 3 days after | 6 months after | I year after |
| | treatment | treatment | treatment |
| Conservative group (%) (28 cases) PTED group (%) (52 cases) | $\begin{array}{c} \textbf{65.80} \pm \textbf{7.86} \\ \textbf{87.64} \pm \textbf{5.82} \end{array}$ | $\begin{array}{c} \textbf{66.20} \pm \textbf{8.20} \\ \textbf{88.35} \pm \textbf{6.12} \end{array}$ | $\begin{array}{c} \textbf{66.40} \pm \textbf{7.94} \\ \textbf{88.80} \pm \textbf{5.72} \end{array}$ |
| t | -13.895 | -13.446 | -12.687 |
| P | 0.000 | 0.000 | 0.000 |

Table 3. VAS remission rate day 3, 6 months and 1 year after treatment in the conservative group and PTED group.

Between the conservative group and PTED group, significant differences were detected in VAS remission rate at 3 days, 6 months, and 1 year after treatment, respectively (P < 0.05). No significant difference was detected in VAS remission rate between 3 days, 6 months, and 1 year after treatment in the conservative group (P > 0.05), while significant differences were detected in VAS remission rate between 3 days, 6 months, and 3 days after treatment in the PTED group (P < 0.05). VAS, visual analogue scale; PTED, percutaneous transforaminal endoscopic discectomy.

| Table 4. | JOA | scores | in | the | conservative | group | and | PTED | group | ١. |
|----------|-----|--------|----|-----|--------------|-------|-----|------|-------|----|
|----------|-----|--------|----|-----|--------------|-------|-----|------|-------|----|

| JOA scores | At admission | 3 days after treatment | 6 months after treatment | l year after treatment |
|--------------------|---------------------------|------------------------------|--------------------------------|------------------------------|
| Conservative group | 12.12±2.83 | 23.32 ± 1.03 | 24.00 ± 0.96 | 24.32±0.85 |
| t PTED group | 12.02 ± 2.37 0.167 | 25.04 ± 1.26 -5.955 | 25.85 ± 0.85 -8.706 | 26.02 ± 1.08 -6.933 |
| P | 0.867 | 0.000 | 0.000 | 0.000 |

Between the conservative group and PTED group, significant differences were detected in JOA scores at 3 days, 6 months, and 1 year after treatment, respectively (P < 0.05), except at admission (P > 0.05). Significant differences were detected in JOA scores between admission, 3 days, 6 months, and 1 year after treatment in the conservative group (P < 0.05) and the PTED group (P < 0.05). JOA, Japanese Orthopaedic Association; PTED, percutaneous transforaminal endoscopic discectomy.

to the VAS score at admission, and all 3 patients' symptoms were derived from a single absolutely responsible nerve root. These 3 patients were then treated with single-segment PTED.

Assessment of clinical symptoms

VAS, JOA score, and ODI results were compared between admission and day 3, 6 months and 1 year after conservative treatment or PTED (Tables 3, 4, and 5).

Discussion

The pathogenesis of lumbar lateral recess stenosis includes narrowing of the

intervertebral disc and segmental instability that has been primarily attributed to age, disc degeneration, loss of nucleus pulposus moisture, fiber ring break, and decreased load capacity of the disc.⁷ The compensatory response results in hypertrophy of small joint and ligamentum flavum, and osteophyte formation of the posterior margin of the vertebral body combined with a bulged fibrous annulus, causing lumbar lateral recess stenosis. Surgical treatment should be considered when the symptoms are severe and nonoperative treatments have failed.⁸

The surgical treatment primarily decompresses the lateral recess of the responsible segment, loosens the compressed nerve, and ensures the stability of the spine, thereby

| ODI scores | At admission (%) | 3 days after treatment (%) | 6 months after treatment (%) | l year after treatment (%) | |
|--|---|---|--|---|--|
| Conservative group PTED group t P | $54.40 \pm 11.87 \\ 55.53 \pm 13.31 \\ -0.358 \\ 0.721$ | $\begin{array}{c} \textbf{20.34} \pm \textbf{2.19} \\ \textbf{17.58} \pm \textbf{8.00} \\ \textbf{0.000} \\ \textbf{0.021} \end{array}$ | $17.68 \pm 1.80 \\ 15.20 \pm 7.25 \\ 0.000 \\ 0.020$ | $\begin{array}{c} 15.76 \pm 2.60 \\ 13.60 \pm 6.20 \\ 2.194 \\ 0.031 \end{array}$ | |

Table 5. ODI scores in the conservative group and PTED group.

Between the conservative group and PTED group, significant differences were detected in ODI scores at 3 days, 6 months, and I year after treatment, respectively (P < 0.05), except at admission (P > 0.05). Significant differences were detected in ODI scores between admission, 3 days, 6 months, and I year after treatment in the conservative group (P < 0.05) and the PTED group (P < 0.05). ODI, Oswestry Disability Index; PTED, percutaneous transforaminal endoscopic discectomy.

alleviating the symptoms of the patient. However, the current surgical procedure for lumbar lateral recess stenosis consists of a posterior median approach for facetectomy and lateral recess decompression, which in turn obliterates the stable structure of the spine. Thus, lumbar fusion and internal fixation should be performed simultaneously,^{9,10} inevitably increasing the duration of the operation and related risks,¹¹ especially when multi-segment surgery is required.¹²

Therefore, the ideal treatment for multisegment lumbar recess stenosis should include local anesthesia, a short procedure, no internal fixation, and minimal invasiveness. Local anesthesia can avoid several adverse factors caused by general anesthesia, such as slow recovery, aspiration pneumonia, and retinal detachment due to high pressure to the eyes, while a short procedure can reduce the intraoperative and postoperative complications. Surgery without internal fixation can reduce the amount of surgical trauma and bleeding, and shorten the operative time. Also, it can avoid the screw loosening caused by low bone density in cases where internal fixation is used.

In recent years, with the rapid development of image guidance equipment and interventional therapy, SNRB has been widely adopted in clinical practice, achieving satisfactory results with minimally invasiveness.¹³ This method involves puncturing the suspected responsible nerve root and injecting the block agent under the guidance of imaging equipment. The mechanisms for the effectiveness of SNRB¹⁴⁻¹⁶ are as follows: first, the local anesthetics are injected to achieve analgesic effects by blocking the neurological activity that produces pain; second, glucocorticoid administration exerts anti-inflammatory and immunosuppressive effects by inhibiting prostaglandin synthesis, reducing nociceptor stimulation and sensitization bv decreasing the release of inflammatory mediators and immune substances. Conversely, it can also alleviate the congestion and edema of the nerve root and play an indirect role in decompressing and increasing the blood supply of the nerve root to improve the treatment of root neuralgia and improve the patients' symptoms.

SNRB not only exerts a therapeutic effect when the diagnosis is unclear, especially in elderly patients with multi-segment lumbar spinal stenosis, but it also has a diagnostic value¹⁷ and positive predictive value.¹⁸ When the puncture needle touches the suspected responsible nerve root, the symptoms might be reproduced during the procedure (first confirmation) and relieved immediately as the analgesic anti-inflammatory agent is injected (second confirmation). Of the 80 patients in this study, 57 patients (71%) had a single absolutely responsible nerve root, 20 patients had 2 relatively responsible nerve roots (25%), and 3 patients had 3 corresponding responsible nerve roots based on the VAS_{-2h} remission rate.

After determining the responsible segment, the next step is decision of the treatment plan based on the block effect after 3 days by SNRB's "diagnosis-treatment". By assessing the VAS_{-3d} remission rate in 57 cases of the single absolutely responsible nerve root, only 16 (28%) patients had good efficacy and continued conservative treatment, while 41 (72%) patients underwent single-segment PTED because of severe nerve entrapment; in 20 cases of 2 relatively responsible nerve roots, 10 (50%) cases continued conservative treatment, and the other 10 (50%) cases underwent double-segment PTED; in 3 cases of 3 relatively responsible nerve roots, 2(67%) cases were conservatively treated, and 1 (33%)treated with three-segment case was PTED. In addition, for those 16 patients continued conservative treatment who with a single absolutely responsible nerve root, 3 patients developed recurrent symptoms in the next year, and then all 3 patients were treated with single-segment PTED.

SNRB clarifies the specifically responsible nerve root. To obtain accurate results, the following points were followed during the procedure: 1) Positioning of the puncture needle tip outside the intervertebral foramen (the position where the nerve root passes through the intervertebral foramen). Moreover, the intervertebral foramen was not be penetrated, because the solution does not act on other nerve roots, thereby improving the accuracy of the diagnosis. 2) For the agent volume of SNRB, Furman, et al.¹⁸ demonstrated that the volume of drug injected is related to the probability of diffusion. When the liquid volume is 0.5 mL, the probability of diffusion is 30%; when the liquid volume is 1 mL, the probability of diffusion is 67%; when the

liquid volume is 1.5 mL, the probability of diffusion is 87%; when the liquid volume is 2 mL, the probability of diffusion is 90%. Therefore, for diagnosing multi-segment lumbar lateral recess stenosis, the recommended drug volume should not exceed 0.5 mL to avoid the effects of liquid on \geq 2 nerve roots simultaneously. Other literature also support the use of 0.5 mL for the diagnosis of SNRB.^{19–21} Thus, 0.5 mL of liquid medicine (0.25 mL of 1% lidocaine and 0.25 mL of betamethasone) was selected for blocking as well as for achieving good results.

With the rapid development in technology, PTED has emerged as a new type of minimally invasive spine surgical method that has the advantages of safety, minimal trauma, and quick recovery. Thus, it is a promising spinal endoscopic technology. Compared with the traditional open surgery for lumbar disc herniation or lumbar spinal stenosis, PTED exhibited the following advantages:²²⁻²⁵ minimally invasive surgery under local anesthesia, which reduced the risk of nerve injury due to communication with awake patients; less damage to the lumbar spinal structure and stability, such as the bone, muscle, ligaments, and other soft tissues; reduced intraoperative and postoperative complications; smaller skin incision of 7-8 mm, less bleeding, shorter operative time and hospital stay, early out of bed functional activities, and rapid recovery, thereby greatly reducing the economic burden for patients.

PTED requires sufficient resection of the superior articular process, foraminoplasty, decompression of the lateral recess, release of the responsible nerve root, and proper removal of hypertrophic ligamentum flavum and herniated disc to further decompress the spinal canal. Three mL of liquid solution, including 2 mL of 0.375% ropiva-caine and 1 mL of betamethasone, was injected around the nerve root before the end of PTED (if surgery on multiple

segments was performed, then 1 mL of betamethasone was evenly distributed according to the segment levels) due to the following benefits: 1) a large volume of liquid can flush the sterile inflammatory mediator around the nerve; 2) a large volume of liquid can be retained for a prolonged period to retain the effect of the block;²⁶ and 3) the anesthetic effect of ropivacaine is more durable than lidocaine.

In summary, the principle involved in the treatment of lumbar degenerative diseases included "stepwise care and treatment". Nowadays, the advantages of minimally invasive treatment for degenerative spinal conditions are becoming more accepted. For multi-segment lumbar lateral recess stenosis, the application of SNRB not only specified the multi-segment lumbar recess stenosis into single-segment, double-segment, and three-segments of responsible nerve roots, but also determined the next treatment plan according to its therapeutic effect. Moreover, some patients were thus spared of the need for surgery. In cases who required surgery, the same therapeutic effect was achieved through minimally invasive surgery such as PTED. Therefore, the application of SNRB and PTED in the treatment of multi-segment lumbar lateral recess stenosis is a minimally invasive, feasible, and effective diagnostic and treatment strategy.

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Declaration of conflicting interest

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