

Clinical Study

Ablation of the basivertebral nerve for treatment of back pain: a clinical study

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Received 9 May 2016; revised 24 August 2016; accepted 29 August 2016

Abstract

BACKGROUND CONTENT: Lumbar axial back pain arising from degenerative disc disease continues to be a challenging clinical problem whether treated with nonsurgical management, local injection, or motion segment stabilization and fusion.

PURPOSE: The purpose of this study was to determine the efficacy of intraosseous basivertebral nerve (BVN) ablation for the treatment of chronic lumbar back pain in a clinical setting.

STUDY DESIGN: Patients meeting predefined inclusion or exclusion criteria were enrolled in a study using radiofrequency energy to ablate the BVN within the vertebral bodies adjacent to the diagnosed level. Patients were evaluated at 6 weeks, and 3, 6, and 12 months postoperatively.

PATIENT SAMPLE: Seventeen patients with chronic, greater than 6 months, low back pain unresponsive to at least 3 months of conservative care were enrolled. Sixteen patients were treated successfully following screening using magnetic resonance imaging finding of Modic type I or II changes and positive confirmatory discography to determine the affected levels. The treated population consisted of eight male and eight female patients; the mean age was 48 years (34–66 years).

OUTCOME MEASURES: Self-reported outcome measures were collected prospectively at each follow-up interval. Measures included the Oswestry Disability Index (ODI), visual analogue scale score, and Medical Outcomes Trust 36-Item Short-Form Health Survey (SF-36).

MATERIALS AND METHODS: This is an industry-sponsored study to evaluate the effectiveness of intraosseous nerves in the treatment of chronic back pain. Consented and enrolled patients underwent ablation of the BVN using radiofrequency energy (INTRACEPT System, Relievent Medsystems, Inc, Redwood City, CA, USA) guided in a transpedicular or extrapedicular approach. Preoperative planning determined targeted ablation zone and safety zones.

RESULTS: Mean baseline ODI of the treated cohort was 52±13, decreasing to a mean of 23±21 at 3 months follow-up ($p<.001$). The statistically significant improvement in ODI observed at 3 months was maintained through the 12-month follow-up. The mean baseline visual analogue scale score decreased from 61±22 to 45±35 at 3 months follow-up ($p<.05$), and the mean baseline physical component summary increased from 34.5±6.5 to 41.7±12.4 at 3 months follow-up ($p=.03$).

CONCLUSION: Ablation of the BVN for the treatment of chronic lumbar back pain significantly improves patients' self-reported outcome early in the follow-up period; the improvement persisted throughout the 1-year study period. Published by Elsevier Inc.

Keywords:

Back pain; Basivertebral nerve; Basivertebral nerve ablation; Electrocautery; Intraosseous nerves; Lumbar; Minimally invasive; Substance P

FDA device/drug status: Approved (Intracapt Flexible Bi-Polar RF Probe and Easy Access Instrument Set).

Author disclosures: **SB:** Relievent Medsystems, Inc. (C), outside the submitted work. **AH:** Nothing to disclose. **MHH:** Royalties: Relievent Medsystems, Inc. (C), outside the submitted work; Consulting: Relievent Medsystems, Inc. (B), outside the submitted work.

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Introduction

This is a report on a clinical series of patients with low back pain, who were treated with a new technology based on percutaneous electrocautery of intraosseous nerves. Although most interventional procedures performed for the treatment of degenerative disease of the spine are directed at the discs or facet joints, very little attention has been paid to possible pain sources within the bone. Many practitioners are unaware that there are nerves within the vertebral body. The literature supports the presence of abundant nerves within the vertebral body, described in detail by Antonacci et al. [1]. Substantial evidence now exists to establish these intraosseous nerves are capable of transmitting nociceptive signals from within the bone.

Intraosseous sources of pain have been well known for a century or more, and would include intraosseous tumors, bone infarcts, and stress fractures. There is also some evidence that elevated intraosseous pressure can cause back pain [2]. The idea that the degenerative process in the spine could result in an intraosseous source of pain becomes very plausible given the observations made by Modic et al. [3] and confirmed by others including Weishaupt et al. and Carragee et al. [4,5] that peri-end plate magnetic resonance imaging (MRI) signal changes, indicative of intraosseous edema or inflammation, can be well correlated with clinical low back pain. The present study was undertaken to evaluate the utility of selective ablation of the intraosseous basivertebral nerves (BVNs) as a new treatment method for patients with chronic low back pain.

The primary source of innervation for the vertebral body are the BVNs that enter the bone of the vertebral body via the large, usually paired, neurovascular foramina that are located at the midline of the posterior cortex, equidistant from each end plate. These nerves accompany the basivertebral artery and vein. This report describes a clinical trial of 16 patients with chronic low back treated with a new minimally invasive procedure using a new minimally invasive bipolar electrocautery device to ablate the intraosseous BVNs within vertebrae adjacent to degenerated discs.

The presence of the intraosseous nerves and their primary site of entry into the human vertebral body through the basivertebral foramen were originally described by Antonacci et al. [1]. These authors established the universal presence of nerves within the basivertebral foramen, and their distribution, which is to course from the midline of the posterior cortex, parallel to the upper and lower end plates, a distance of slightly more than 1/3 of the AP diameter of the vertebral body, at which point the neurovascular bundles bifurcate, with two neurovascular bundles branching obliquely anterolaterally, which initially continue to lie parallel to the end plates. From the point of this initial bifurcation, these nerves branch repeatedly, and these branches are noted to course to all areas within the vertebral body, including areas near the end plates. Immunohistochemical staining has demonstrated that of BVNs harvested from within 76 human

vertebral bodies all were confirmed to contain the pain-associated neurotransmitter substance P [6]. Bailey et al. confirmed this observation and further demonstrated that these intraosseous nerves also stained positive for PGP 9.5, also consistent with a role in pain transmission [7].

Multiple reports support the idea that vertebral end plate nociceptors arborized from the BVN are the principal transmission vehicles for chronic low back pain. Antonacci et al. showed that the vertebral bodies and end plates are innervated principally by the BVN and its branches. These investigators performed a histologic examination of 23 human vertebral bodies and determined the BVN enters the vertebral body through the posterior basivertebral foramen [1]. Further work by Fris et al. examining 62 vertebral bodies found the BVN to stain positive for substance P, suggesting the BVN is a nociceptor or pain-transmitting nerve [6]. Bailey et al. traced the origin of nerves located at the end plate and confirmed that the majority of nerves entered the vertebral body via the posterior basivertebral foramen and their distribution followed the known vascularity patterns within the vertebral body. Staining of the neurofibers with PGP 9.5 also suggested that these nerves have a nociceptive role [7].

Clinical evaluation of patients with discogenic chronic low back pain has been associated with intraosseous MRI changes adjacent to the vertebral end plates as described by Modic [3]. Weishaupt et al. reported 100% specificity to pain on provocative discography associated with moderate to severe type 1 and type 2 Modic changes. Carragee et al. showed that these Modic changes were more strongly associated with continued low back pain than provocative discography [4,5]. Likewise, Rahme and Moussa observed that type I Modic changes were associated with what they termed biomechanical instability and low back pain symptoms [8]. Kuisma et al. determined an odds ratio of 2.28 for Modic changes being present at L5–S1 in patients presenting with low back pain compared with those without Modic changes [9].

Specific evidence of vertebral bone as a source of pain signals was provided by Kuslich et al. who reported on a series of patients who underwent open surgical laminectomy procedures using local anesthesia only. He reported that the direct intraoperative mechanical stimulation of the end plates of these awake patients consistently provoked significant pain response [10].

These observations on the role of the BVN and the transmission of intraosseous pain signals led to the hypothesis that disruption of the BVN signaling pathway could relieve chronic low back pain in selected patients. To test this hypothesis, a clinical protocol was designed to recruit patients with chronic low back pain under specific inclusion and exclusion criteria designed to identify patients with low back pain and Modic type I or II changes. Imaging was used to determine the site of the bifurcation of the BVN in each patient, and RF thermal ablation was used to selectively ablate the BVN of selected vertebral bodies at the affected functional level using a minimally invasive device (INTRACEPT System, Reliant Medsystems, Inc, Redwood City, CA, USA).

EVIDENCE & METHODS

Context

Axial back pain resulting from degenerative changes in the lumbar spine is a challenging clinical entity and is often refractory to interventions including pain medications, therapy and a variety of injections, not to mention surgery. The authors sought to determine the efficacy of basivertebral nerve ablation for the treatment of chronic lumbar back pain in a pilot study.

Contribution

The authors include 17 patients treated with RF energy to ablate the basivertebral nerve within the vertebral bodies adjacent to the painful level. The authors maintain that the treatment improved patient self-reported outcomes and that improvement was largely maintained through the 12-month follow-up period.

Implications

This study, as a proof of concept, shows that the basivertebral nerve does play a role in the development of certain types of axial back pain. As a pilot study, the effort was not designed to be conclusive and the selection criteria should be considered by physicians looking to apply these results in a clinical context. There was also no viable control for the patients treated in this study. As the authors mention, an ongoing randomized study is currently underway which is likely to provide more definitive and informative results. As a result, the current effort should likely be considered Level III evidence.

Materials and methods

Patients with isolated axial low back pain of greater than 6 months' duration non-responsive to at least 3 months of conservative care were recruited for a prospective, single-arm, multicenter, clinical study to evaluate the preliminary safety and effectiveness of the INTRACEPT System for the ablation of BVNs within the vertebral body for the treatment of low back pain. No specific course of conservative care was mandated before enrollment. Exclusion criteria included prior spinal surgery, spondylolisthesis, scoliosis, history of spinal infection, and prior spinal malignancy. Patients who had radicular symptoms were also excluded. The study was also limited to the L3, L4, L5, and S1 vertebrae. Patients with identified pathology at more cephalad levels were excluded. The clinical study was initiated at two centers in the European Union using CE Marked INTRACEPT products following local Integrating Healthcare Enterprise approval and at three sites in the United States using 510(k) cleared INTRACEPT products following local institutional review board approval. Diagnosis of the treatment level(s) was made by clear evidence of type 1 or 2 Modic changes as seen on MRI, or

established by provocative discography. For subjects who presented with Modic changes, positive discography was optional; for subjects who did not present with Modic changes, provocative discography was required to confirm the target level(s). Treatment was limited to two or three contiguous vertebral bodies, representing one or two motion segments, respectively. A detailed history and physical examination was performed on each patient to exclude origins of pain such as sacroiliac joint, hip, myofascial, genitourinary, gastrointestinal, or gynecologic sources.

In addition to assisting in determination of the affected (treatment) levels, the preoperative MRI was used for targeting, that is, to identify the intraosseous site of bifurcation of the BVN within the vertebral bodies intended for treatment. Transverse and sagittal views were used to determine the precise location of the BVN bifurcation based on MRI (Fig. 1).

A cannulated access system was used for either transpedicular or extrapedicular unilateral access of each vertebral body to be treated. The vertebral bodies above and below the painful motion segment were treated. A radiofrequency (RF) energy delivery system (INTRACEPT System) capable of thermally ablating an approximate spherical region of 10-mm diameter (5-mm radius) was guided to the predetermined target (BVN terminus) under fluoroscopic imaging; the RF probe which contained a thermal sensor was 2 mm in diameter. A fixed 10-mm safety margin was established in the treatment protocol to provide a protective margin for the posterior structures. That is, the selected target and the final position of the tip of the RF probe was required to end at least 10 mm anterior to the posterior wall of the vertebral body (Fig. 2). Each treated vertebral body was heated locally at the terminus of the BVN to 85°C for 15 minutes. Before beginning the pilot clinical study, dose and extent mapping of the ablation zone was performed in a bovine model. The parameters selected created an approximately 1-cm diameter roughly spherical ablation zone. An independent core laboratory (Medical Metrics, Houston, TX, USA) determined whether or not the predetermined targeting was achieved and evaluated the safety of the created lesions with respect to critical anatomical structures.

Self-reported outcomes instruments were used to assess patients' condition preoperatively and at each follow-up time point. The Oswestry Disability Index (ODI), Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and the visual analogue scale (VAS) for pain were administered preoperatively and at 6 weeks, 3 months, 6 months, and 12 months postoperatively. Additional MRI imaging was performed at each follow-up visit. Confirmation of targeting success or failure was measured on the 6-week MRI Add figure. Neurologic examination and adverse event screening and reporting was also performed at each follow-up interval.

Patient success following treatment was as assessed by (1) improvement in patient disability as defined by the ODI; (2) maintenance of baseline neurologic status as determined by focused neurologic examination; and (3) no device or surgical procedure-related serious adverse events. Additional



Fig. 1. Sagittal (Left) and transverse (Right) view of the lumbar spine on magnetic resonance imaging (MRI). The posterior origin and approximate mid-body terminus of the basivertebral nerve (BVN) may be estimated.

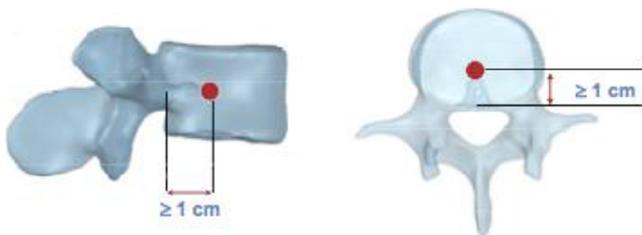


Fig. 2. Illustration of preoperative planning for targeting the area to be ablated. A safe zone with a minimum of 10-mm distance is required from the posterior wall of the vertebral body to the peripheral margin of the ablation legion.

secondary end points of the study included (1) probe placement verification; (2) pain evaluation as measured by the VAS; and (3) general health and quality of life status as measured by the Medical Outcomes Study SF-36.

Results

A total of 17 patients were enrolled in the clinical trial; 16 of the patients were treated with the INTRACEPT System. The study was designed to be a pilot study which could be used to power a randomized controlled trial based on the observed change in outcome variables and the respective standard deviations. One patient was enrolled, but not treated, when he was found to have bony anatomy not conducive to satisfactory probe placement with the non-steerable instrumentation available early in the study. In this patient, the device was therefore not turned on, and the device was withdrawn. No RF energy was delivered in this patient; steerable instrumentation was subsequently designed, and all subsequent patients were successfully targeted. Therefore, data are reported on this cohort of 16 patients. The mean age was 48 years (34–66), and the mean body mass was 86 kg (68–114); there were 8 men and 8 women in the cohort. In 14 out of 16 patients, the affected levels were identified solely using Modic changes; the remaining 2 patients also underwent confirmatory positive discography. Fourteen subjects were treated at two vertebral bodies (one motion segment) and two subjects were treated at three vertebral bodies (two motion segments). A transpedicular access was used in 68% of the levels accessed and an extrapedicular access was used in the remaining 32%. All 16 subjects completed the 12-month follow-up course of study and were evaluated for all efficacy and safety end points.

The primary efficacy end point for this study was the improvement in subject measured disability from baseline as defined by the ODI. Mean baseline ODI of the treated cohort was 52 ± 13 , decreasing to a mean of 23 ± 21 at 3 months follow-up ($p < .001$). This result was sustained throughout the 1-year study follow-up with statistically significant improvement in subject reported pain and low back pain-specific disability at all study follow-up points with a more than 28 point improvement in the mean ODI score (Fig. 3). These ODI outcomes were more than double the preplanned threshold set for demonstration of efficacy in the primary end point, defined as a minimally clinically important change in ODI of a 10-point decrease as reported by Hagg et al. and Ostelo and de Vet [11, 12].

The mean baseline VAS decreased from 61 ± 22 to 38 ± 30 and 45 ± 35 at 6 weeks and 3 months follow-up, respectively ($p < .05$). The mean baseline physical component summary increased from 34.5 ± 6.5 to 44 ± 11 and 41.7 ± 12.4 at 6 weeks and 3 months follow-up, respectively ($p = .03$).

The fixed 10-mm safety zone was not violated in any of the 34 treated vertebrae as determined by external review by the independent core laboratory (Medical Metrics). The overall measured distance between the center of the lesion and the posterior wall of the vertebral body in the 34 treated

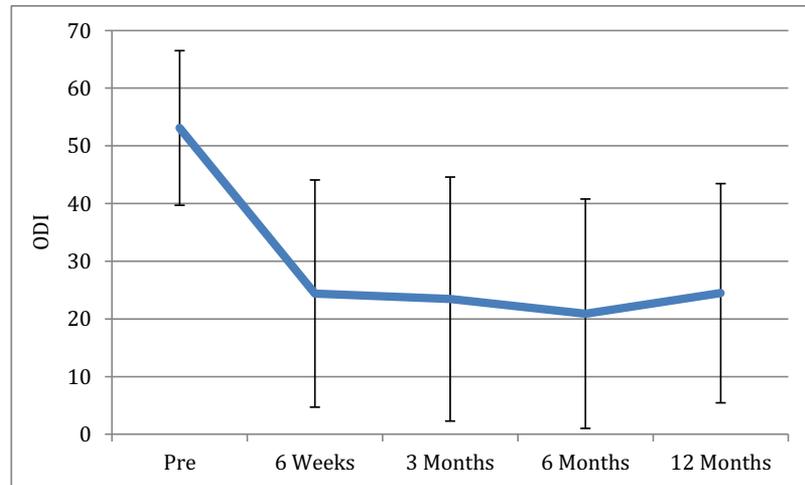


Fig. 3. Evolution of Oswestry Disability Index (ODI) over time in the 16 patients treated with basivertebral nerve (BVN) ablation, statistically significant ($p < .001$) at each time point compared with baseline. Minimum clinically significant improvement is 10 points of ODI change.

vertebrae was 13.5 mm, with a range of 10–18 mm; all measured distances from the lesion centers exceeded the minimum safety zone distance of 10 mm. Ablation targeting success was also measured and determined to be on target in 31 of 34 levels (91%). Extrapedicular access was used when a straight transpedicular path to the estimated BVN terminus location was not possible; near the end of the study, curved instrumentation permitting broader access from a transpedicular entry was made available.

Representative lesions created in the vertebral body are shown in Fig. 4. The RF probe creates an approximately 1-cm diameter spherical ablation zone which is centered on the bifurcation of the BVN interoperatively using fluoroscopy.

All 16 treated patients maintained their functional neurologic status throughout the entire course of the 12-month study follow-up. Minor, clinically insignificant, neurologic changes were noted in six patients. In four of these six cases, the changes were not believed to be related to the INTRACEPT treatment, and these four patients had no functional deficits.

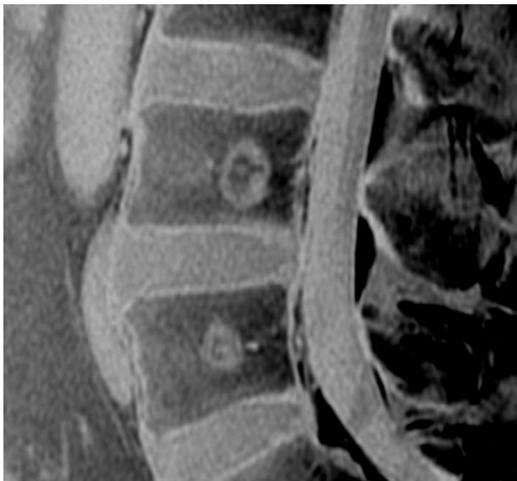


Fig. 4. Representative ablation zones at L4–L5 as seen on sagittal reconstruction at 6 weeks follow-up.

In the remaining two cases, the observed minor changes may have possibly been related to the INTRACEPT treatment; however, neither of these patients had any functional deficits.

There were no device- or procedure-related serious adverse events in the study. Four non-serious, device- or procedure-related adverse events were reported in the immediate postoperative period; none of these events required significant intervention other than pain medication. These events included buttock pain, lumbar pain, dysesthesia, and mild transient thigh numbness thought to be caused by prone positioning on the procedure table.

Two patients required surgical intervention late during the follow-up period for spine-related complaints that were not related to the INTRACEPT treatment. One patient reported leg and back pain (>9 months posttreatment) that was initially treated with drug therapy and physical therapy. Following persistent pain, a subsequent MRI showed a disc herniation at L4–L5, which was successfully treated by a microdiscectomy. A second patient reported new onset of pain (>7 months posttreatment) caused by a new L4–L5 posterolateral disc herniation, documented by an MRI study. A microdiscectomy was performed and the patient's symptoms resolved.

There were no access-related complications reported following the procedures. There were no reports of burns, nor other thermal or non-thermal injuries related to the delivery of RF energy within the vertebral body. None of the patients reported were observed by the independent core laboratory to have had a compression fracture during the course of the study.

The overall patient treatment success using the pre-defined criteria at 12 months was 13 of 16 patients or 81%. The three patients not meeting the combined study success criteria failed to exhibit significant ODI improvement.

Discussion

These data strongly suggest that the BVN plays a substantial role in the transmission of pain signals in patients with

chronic low back pain and that vertebral denervation via ablation of the BVN may have significant therapeutic benefit in carefully selected patients. More than 80% of patients were considered a clinical success, and a statistically significant decrease in ODI was observed at all time intervals through 1-year follow-up.

Surgical intervention for the treatment of chronic low back by the fusion of degenerated or “unstable” motion segments pain is a commonly used therapy. However, the reported outcomes observed are decidedly mixed and are the focus of ongoing controversy. Bydon et al. recently performed a meta-analysis of randomized controlled trials performed comparing fusion versus nonoperative management of discogenic low back pain [13]. They found that although there was a 7.4 point lower ODI in the operated than the nonoperated group, the difference was not statistically significant. Another recent study summarizing a number of randomized studies comparing surgical fusion with conservative care for the treatment of low back pain found no difference in outcome, again suggesting that alternative mechanisms of pain generation and alleviation must be investigated [14].

Although the mechanisms and pathways and the origin and treatment of back pain associated with degenerative changes in the intervertebral disc have been studied for some more than half a century, alternative mechanisms of back pain must also be investigated, given that a recent study has revealed that low back pain is now the most common source of disability worldwide [15]. The existence of intraosseous sources of back pain now cannot be disputed. The new technique reported here appears to be a promising option in carefully selected patients.

Conclusion

The 1-year data from this clinical series suggest that BVN ablation is an effective means of improving outcomes in selected patients with chronic low back pain. Further determination of the effectiveness of BVN ablation to treat chronic low back pain is presently being evaluated in an ongoing randomized clinical trial (FDA RCT NCT01446419).

Acknowledgment

The contributions of Mark Belza, MD, Charles Gordon, MD, Guy Danielson III, MD, Aaron K. Calodney, MD, and Allen Carl, MD to the execution of the study are

acknowledged. The study was funded by Relievable Medsystems, Redwood City, CA.

References

- [1] Antonacci MD, Mody DR, Heggeness MH. Innervation of the human vertebral body: a histologic study. *J Spinal Disord* 1998;11:526–31.
- [2] Esses SI, Moro JK. Intraosseous vertebral body pressures. *Spine J* 1992;17:S155–9.
- [3] Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology* 1988;166(1 pt 1):193–9.
- [4] Weishaupt D, Zanetti M, Hodler J, et al. Painful lumbar disk derangement: relevance of endplate abnormalities at MR imaging. *Radiology* 2001;218:420–7.
- [5] Carragee EJ, Alamin TF, Miller JL, Carragee JM. Discographic, MRI and psychosocial determinants of low back pain disability and remission: a prospective study in subjects with benign persistent back pain. *Spine J* 2005;5:24–35.
- [6] Frasc C, Kravetz P, Mody DR, Heggeness MH. Substance P-containing nerves within the human vertebral body: an immunohistochemical study of the basivertebral nerve. *Spine J* 2003;3:63–7.
- [7] Bailey JF, Liebenberg E, Degmetich S, Lotz JC. Innervation patterns of PGP 9.5-positive nerve fibers within the human lumbar vertebra. *J Anat* 2011;218:263–70.
- [8] Rahme R, Moussa R. The Modic vertebral endplate and marrow changes: pathologic significance and relation to low back pain and segmental instability of the lumbar spine. *AJNR Am J Neuroradiol* 2008;29:838–42.
- [9] Kuisma M, Karppinen J, Niinimäki J, et al. Modic changes in endplates of lumbar vertebral bodies: prevalence and association with low back and sciatic pain among middle-aged male workers. *Spine* 2007;32:1116–22.
- [10] Kuslich SD, Ulstrom CL, Michael CJ. The tissue origin of low back pain and sciatica: a report of pain response to tissue stimulation during operations on the lumbar spine using local anesthesia. *Orthop Clin North Am* 1991;22:181–7.
- [11] Hagg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. *Eur Spine J* 2003;12:12–20.
- [12] Ostelo RW, de Vet HC. Clinically important outcomes in low back pain. *Best Pract Res Clin Rheumatol* 2005;19:593–607.
- [13] Bydon M, De la Garza-Ramos R, Macki M, Baker A, Gokaslan ZL, Bydon A. Lumbar fusion versus non-operative management for treatment of discogenic low back pain: a systematic review and meta-analysis of randomized controlled trials. *J Spinal Disord Tech* 2014;27:297–304.
- [14] Hedlund R, Johansson C, Hagg O, Fritzell P, Tullberg T. The long-term outcome of lumbar fusion in the Swedish lumbar spine study. *Spine J* 2016;16:579–87.
- [15] Martin BI, Deyo RA, Mirza SK, et al. Expenditures and health status among adults with back and neck problems. *JAMA* 2008;299:656–64.