

Clinical efficacy of transforaminal percutaneous endoscopic lumbar discectomy combined with ozone therapy for the treatment of lumbar disc herniation: comparison with fenestration discectomy. A prospective study

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Key words: transforaminal percutaneous endoscopic lumbar discectomy; lumbar disc herniation: comparison; clinical efficacy; fenestration discectomy.

Abstract. The aim of this prospective study was to investigate the clinical efficacy of the transforaminal percutaneous endoscopic lumbar discectomy (PELD), combined with ozone in the treatment of lumbar disc herniation, and to compare its short-term efficacy with fenestration. The study included 109 adult patients admitted to our hospital from January 2015 to December 2016 that met the inclusion criteria. All patients were randomly divided into two groups: the combination group and the fenestration group. The visual analogue scale (VAS) was used to measure postoperative pain of the surgical wound and waist and leg. The JOA score was used to measure recovery status, and the Oswestry disability index (ODI) was used to determine lumbar dysfunction. The operation time and hospitalization time in the combined group were significantly shortened, and the average blood loss and the average amount of intervertebral disc resection were also significantly lower than those in the fenestration group. At all-time points, the VAS score of postoperative pain in the combined group was significantly lower than that in the control group. VAS and ODI scores were significantly decreased and JOA scores were significantly higher in the combined group. The treatment rate in the combined group was significantly higher than that in the open window group. However, there was no a significant difference in the incidence of complications between the two groups. PELD combined with ozone therapy can significantly improve the therapeutic effects and shorten the recovery time of patients with lumbar disc herniation, but does not affect the incidence of postoperative complications.

Eficacia clínica de la discectomía lumbar endoscópica percutánea transforaminal, combinada con ozonoterapia, en el tratamiento de la hernia de disco lumbar: comparación con la discectomía por fenestración. Un estudio prospectivo.

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Palabras clave: discectomía lumbar endoscópica percutánea transforaminal; hernia de disco lumbar: comparación; eficacia clínica; discectomía de fenestración.

Resumen. Se evaluó la eficacia clínica de la discectomía lumbar endoscópica percutánea (PELD) combinada con ozonoterapia en el tratamiento de la hernia de disco lumbar, y se comparó su eficacia a corto plazo con la fenestración. El estudio incluyó a 109 pacientes adultos, divididos aleatoriamente en: un grupo de combinación, en el que los pacientes recibieron PELD y tratamiento con ozono y un grupo tratado mediante fenestración. La escala analógica visual (VAS) se utilizó para medir el dolor postoperatorio de la herida quirúrgica y el de la cintura y la pierna. La escala JOA se usó para medir el estado de recuperación, y el índice de discapacidad de Oswestry (ODI) para determinar la disfunción lumbar. Los tiempos de operación y de hospitalización en el grupo combinado se redujeron significativamente, y los promedios de pérdida de sangre y la cantidad de resección del disco intervertebral también fueron significativamente más bajas que las del grupo de fenestración. La puntuación VAS de dolor postoperatorio en el grupo combinado fue significativamente menor que en el grupo control. Los puntajes VAS y ODI disminuyeron significativamente y los puntajes JOA fueron significativamente más altos en el grupo combinado. La tasa de tratamiento en el grupo combinado fue significativamente mayor que la del grupo de ventana abierta. Sin embargo, no hubo diferencias significativas en la incidencia de complicaciones entre los dos grupos. La PELD combinada con la ozonoterapia puede mejorar significativamente el efecto terapéutico y acortar el tiempo de recuperación de los pacientes con hernia de disco lumbar, pero no afecta la incidencia de complicaciones postoperatorias.

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INTRODUCTION

Lumbar disc herniation, a common disease caused by the compression of spinal nerve roots, affects a huge amount of population worldwide (1, 2). The low back pain and radicular sciatica are the main symptoms for lumbar disc herniation, in which 1.6-43% patients with low back pain are associated

sciatic symptoms, and 90% of the cases are caused by disk herniation (3-5). The transforaminal percutaneous endoscopic lumbar discectomy (PELD), a target oriented technique, is now widely used and considered as an efficacious, minimally invasive procedure for soft disc herniation (6). Studies show PELD has the advantages of preservation of posterior structures, smaller incision, less

paravertebral muscle injury, and a similar effectiveness compared with the traditional open discectomy (7, 8). Besides the application of PELD, the use of ozone (O₃) therapy is also reported to be effective in treatment of lumbar disc herniation (9). Ozone is a strongly oxidant gas with antiseptic, immunomodulating, analgesic and anti-inflammatory properties and ozone treatment is also widely used in the treatment of inflammatory and degenerative processes, as well as nociceptive-neuropathic pain, including disc herniation (10, 11).

Despite the studies of PELD and ozone therapy, to our best of knowledge, few studies used the combination of PELD and ozone therapy in treatment of disc herniation, and few studies compared the clinical effective between the combination of PELD and ozone therapy with the fenestration discectomy using prospective strategy in treatment of lumbar disc herniation. In the present study, we conducted a randomized controlled prospective study to investigate the clinical efficacy of transforaminal percutaneous endoscopic lumbar discectomy combined with ozone therapy for the treatment of lumbar disc herniation, and compared its short-term efficacy with fenestration discectomy. This study might provide more clinical evidences for the efficacy and safety of PELD and ozone therapy in the treatment of lumbar disc herniation.

METHODS AND MATERIALS

Patients and treatment

In this prospective study, a total of 109 adult patients who went to our hospital and conformed to the inclusion criteria during January 2015 to December 2016 were included. All patients were diagnosed as lumbar disc herniation and confirmed by X-ray, CT or MRI. The patients had received conservative treatment for more than three months; however the pain of waist and legs didn't reduce or recurred. The following patients were excluded: patients with opera-

tive history of lumbar spine, patients with other fracture and sprain, and patients with lumbar spinal stenosis, vertebral fractures, spondylolisthesis, thickening of ligamentum flavum, spinal tumors, spinal tuberculosis, moderate to severe osteoporosis or ankylosing spondylitis. All patients were randomly divided into two groups, 1) the combined group (n=55), in which patients received PELD and ozone treatment; 2) the fenestration group (n=54), in which patients received traditional fenestration surgery. Written informed consent was obtained from all patients within 24 h of admission. The present study was approved by ethic committee of Wuhan Puai Hospital.

Surgical technique

For the combined group, surgery procedure was performed as described previously (12, 13). Briefly, the patient was in the prone position and under local anesthesia. After observing by C-arm fluoroscopy (Perlong Medical Devices Co., Ltd., Nnanjing, China), an incision was made at 6~10 cm beside the horizontal position of the middle line for L2-L3 and L3-L4 segments, and was made at 12~14 cm beside the horizontal position of the middle line for L4~L5 and L5~S1 segments. After gently insertion of an 18-gauge spinal needle, infiltration anesthesia was conducted using 3 mL 1% lidocaine and 2 mL 5% lidocaine was used for further anesthesia after the needle reached the superior articular process. Then intraoperative discography was performed with a mixture of contrast agent and methylene blue to stain the pathological nucleus and estimate the location of the annular tear. Then a guide wire was inserted through the spinal needle to confirm the position, and the needle was then removed. After placed the bushing, the foraminoplasty was performed by cutting off part of sclerotin outer margin of articular process and the intervertebral foramen was expanded. Then the trephine was moved and a transforaminal endoscope was placed into the bushing. The degenerated nucleus

pulposus was moved by nucleus pulposus forceps and the damaged fibrous annulus was repaired by dual frequency RF electrode. Then the bushing and the transforaminal endoscope were moved and the incision was sutured. For ozone treatment, all patients received injection of 10 mL O₃ (60 µg/mL, generated by ozone generator, Herrmann Ltd. Germany) into the intervertebral disc lesion after surgery, the dose was mainly according to our clinical experience.

The standard fenestration surgery was conducted as described in many studies (14, 15). Briefly, after anesthesia, a middle incision was made at a posterior position of the responsible vertebra and another incision was made at the position of the lumbar spinous process of lumbar lesions. After gradually cutting the skin, subcutaneous tissue and back fascia, the paraspinal muscles were slowly peeled off and the vertebral plate protruding side and horizontal position of the articular process of the lesion were exposed. After observing by C-arm fluoroscopy (Perlong Medical Devices Co., Ltd., Nnanjing, China), the lower edge of the upper vertebral plate was moved by laminectomy forceps and the fenestration was conducted. Extended decompression of nerve root canal was performed if necessary. After the nerve root and thecal sac were exposed and separated, the intervertebral disc tissues were seen clearly and the degenerated nucleus pulposus, injured fibrous ring and the proliferative tissues around the lesion were all removed. Then the surgery incisions were washed by normal saline. Then drainage-tube was placed and the incision was sutured. All treatment was conducted by the same group according to the same treatment protocol.

Measurement and Data collection

Demographic data and clinical variables such as age, segment of intervertebral disc protrusion, pathological types, course of disease, as well as surgery time, intraoperative blood loss, discectomy volume and hospitalization time were collected. The visual ana-

logue scale (VAS) was used to measure the postoperative pain condition at 1 h, 12 h, 24 h and 48 h after surgery. The postoperative pain condition of lumbar and legs of the patients were also measured using VAS scores at 1 month, 3 months and 6 months after surgery. The Japanese Orthopaedic Association (JOA) score was used to measure the recovery condition. The Oswestry disability index (ODI) was used to determine the lumbar dysfunction at 1 month, 3 months and 6 months after surgery. A modified MacNab criteria was used to evaluate the efficacy of the treatment at 6 months after surgery as described elsewhere (16). The postoperative complications were also recorded. All patients were followed-up for 6 months.

Statistical analysis

The measurement data were expressed by mean ± SD. Chi square test was used to compare the counting materials and rates. Comparison between two groups of continuous data was performed using the Student *t*-test. It was considered to be statistically significant when *P*-value was less than 0.05. All calculations were made using SPSS 18.0.

RESULTS

Basic clinical characteristics for all patients

The present study included a total of 109 patients, with a mean age of 56.7±10.6, male: female ratio was 62: 47, and disease course duration 3.1±1.5. As shown in Table I among all patients, L3~L4 intervertebral disc herniation included 28 cases (25.7%), and L4~L5 segment 54 cases (49.5%), L5~S1 27 cases (24.8%). Meanwhile, 35 cases (32.1%) were diagnosed as central disc herniation, 61 cases (56.0%) as paracentral disc herniation and 13 cases (11.9%) as posterolateral disc herniation. No significant difference was observed between the combined and the control groups. The study flow chart is shown in Fig. 1.

TABLE I
BASIC CLINICAL CHARACTERISTICS FOR ALL PATIENTS

| Variables | Combined group n=55 | Fenestration group n=54 |
|--|------------------------|----------------------------|
| Age, year | 56.4±11.1 | 57.2±10.3 |
| Gender, male: female | 32: 23 | 30: 24 |
| Course of disease, year | 3.1±1.4 | 3.2±1.3 |
| Segment of intervertebral disc herniation, n (%) | | |
| L3~L4 | 16 (29.1) | 12 (22.2) |
| L4~L5 | 26 (47.3) | 28 (51.9) |
| L5~S1 | 13 (23.6) | 14 (25.9) |
| Pathological types, n (%) | | |
| Central | 17 (30.9) | 18 (33.3) |
| Paracentral | 32 (58.2) | 29 (53.7) |
| Posterolateral | 6 (10.9) | 7 (13.0) |

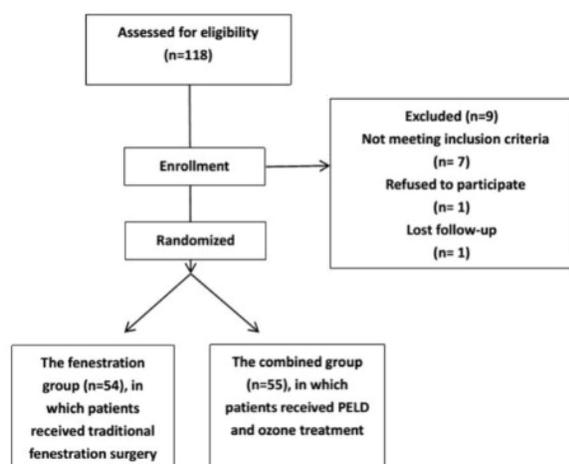


Fig. 1. The study flow chart.

To further compare the difference between PELD combined with ozone treatment and the fenestration discectomy, the intraoperative indexes were collected and analyzed. Results showed that the surgery time and hospitalization time of the combined group were both significantly shorter than those of the fenestration group ($P < 0.05$, Table II). Besides, the mean blood loss and the mean discectomy volume of the combined group were also significantly less than those of the fenestration group ($P < 0.05$). These results suggested the PELD combined with ozone treatment had shorter surgery time, smaller operative injury and shorter hospitalization duration than the fenestration discectomy.

TABLE II
COMPARISON FOR SURGERY TIME, INTRAOPERATIVE BLOOD LOSS, DISCECTOMY VOLUME AND HOSPITALIZATION TIME BETWEEN THE TWO GROUPS.

| Variables | Combined group, n=55 | Fenestration group, n=54 | P |
|-------------------------------|----------------------|--------------------------|--------|
| Surgery time, min | 129.4±24.1 | 156.7±28.4 | <0.001 |
| Intraoperative blood loss, ml | 67.3±22.6 | 151.4±31.9 | <0.001 |
| Discectomy volume, g | 3.1±1.1 | 4.6±1.3 | <0.001 |
| Hospitalization time, d | 11.2±3.4 | 17.5±4.7 | <0.001 |

The postoperative pain of operative wound between the two groups was measured by VAS scores at 1 h, 12 h, 24 h and 48 h after surgery. As shown in Table III, at all the time points, the VAS scores of the combined group were significantly lower than the fenestration group ($P<0.05$), showing the postoperative pain of the operative wound was significantly lower for PELD combined with ozone treatment.

The recovery condition was evaluated by VAS and JOA scores for pain condition of lumbar and leg and ODI scores for lumbar dysfunction. Results showed before the surgery; all the three indexes showed no significant difference between the two groups. After treatment for 1 month, the VAS and ODI scores gradually decreased and the JOA scores gradually increased in both groups. However, the VAS scores and ODI scores were both significantly lower in the combined group at all the time points after surgery

($P<0.05$, Table IV, and the JOA scores were significantly higher in the combined group. These results indicating the PELD combined with ozone treatment results in better short-term recovery for lumbar disc herniation.

At last, we compared the short-term efficacy and postoperative complications between the two groups at 6-month affect surgery. As shown in Table V, the treatment well rate (good and excellent) for combined group was significantly higher than the fenestration group ($P<0.05$). However, the complication rates for the two groups showed no significant difference.

DISCUSSION

Low back pain, which is mainly caused by disc herniation, is one of the most common and important clinical and public health problems worldwide. Though several studies have demonstrated the application of PELD

TABLE III
COMPARISON FOR POSTOPERATIVE PAIN OF OPERATIVE WOUND BETWEEN THE TWO GROUPS.

| VAS scores | Combined group, n=55 | Fenestration group, n=54 | P |
|------------|----------------------|--------------------------|--------|
| 1 h | 4.5±2.1 | 7.3±3.0 | <0.001 |
| 12 h | 3.4±1.2 | 6.2±2.5 | <0.001 |
| 24 h | 2.6±1.0 | 5.6±1.9 | <0.001 |
| 48 h | 1.9±0.9 | 4.0±1.3 | <0.001 |

TABLE IV
COMPARISON FOR RECOVERY AT 1 MONTH, 3 MONTHS AND 6 MONTHS BETWEEN THE TWO GROUPS.

| Variables | Group | Before treatment | 1 mon | 3 mon | 6 mon |
|-----------|--------------------|------------------|-------------|-------------|-------------|
| VAS | Combined group | 6.3±2.1 | 4.6±1.4*.# | 2.8±1.1*.# | 1.7±0.8*.# |
| | Fenestration group | 6.5±2.3 | 5.5±1.6# | 4.6±1.3# | 3.5±1.2# |
| ODI | Combined group | 0.9±0.3 | 0.6±0.2*.# | 0.4±0.1*.# | 0.2±0.1*.# |
| | Fenestration group | 0.9±0.2 | 0.8±0.2# | 0.6±0.2# | 0.5±0.2# |
| JOA | Combined group | 11.6±2.6 | 17.9±3.1*.# | 21.4±3.3*.# | 23.6±3.5*.# |
| | Fenestration group | 11.3±2.2 | 13.8±2.3# | 15.9±2.3# | 17.7±2.5# |

* $P<0.05$, compared with the fenestration group; # $P<0.05$, compared with the value before surgery.

TABLE V
COMPARISON FOR TOTAL EFFICACY AND POSTOPERATIVE COMPLICATIONS BETWEEN THE TWO GROUPS.

| Variables | Combined group, n=55 | Fenestration group, n=54 | P |
|----------------------------|----------------------|--------------------------|-------|
| MacNab criteria, n (%) | | | 0.018 |
| Excellent | 27 (49.1) | 22 (40.7) | |
| Good | 23 (41.8) | 18 (33.3) | |
| Fair | 4 (7.3) | 10 (18.5) | |
| Poor | 1 (1.8) | 4 (7.4) | |
| Complications, n (%) | | | 0.628 |
| Limb sensory abnormalities | 1 (1.8) | 2 (3.7) | |
| Laceration of endorachis | 1 (1.8) | 1 (1.9) | |

in the treatment of lumbar disc herniation, no study has reported the efficacy of PELD combined with ozone injection, and few studies focused on comparison between PELD and fenestration discectomy. In the present research, we investigated the short-term efficacy of PELD combined with ozone injection in treatment of lumbar disc herniation using fenestration discectomy as a control.

Efficacy of PELD in lumbar disc herniation has been reported in several studies. Yong *et al.* studied PELD in treatment of upper lumbar disc herniation; results showed the treatment well rate was 77.8% (17). Zheng *et al.* (18) demonstrated PELD could be also used in treatment of far-lateral lumbar disc herniations in children with an overall success rate of 91.6%). Kim *et al.* (19) showed PELD could be applied comfortably even for less-experienced surgeons for the treatment of highly migrated disc herniation (19). Besides, Ding *et al.* conducted a meta-analysis to compare the treatment efficacy of PELD and fenestration discectomy and found PELD had better efficacy than fenestration discectomy (20). However, in this meta-analysis, most included studies were reported in Chinese and published in Chinese journals, thus a study which has broader influence to show the difference of PELD and fenestration discectomy in treatment of lumbar disc herniation is still needed. In

our research, we for the first time showed the combination use of PELD and ozone treatment could significantly enhance the treatment efficacy and shorten the recovery duration of lumbar disc herniation patients.

The application of ozone in the treatment of lumbar disease has been also reported in some researches. Paoloni *et al.* (21) showed intramuscular oxygen-ozone therapy could be used in the treatment of acute back pain with lumbar disc herniation, which was safe and effective and with minimal invasion. Muto *et al.* (22) also demonstrated oxygen-ozone therapy had high treatment well rate for lumbar disk herniations. Gautam *et al.* (23) reported the successful use of the combined use of oxygen-ozone therapy with percutaneous intradiscal radiofrequency thermocoagulation for the treatment of lumbar disc herniation. In the present study, we also found the combination use of PELD and ozone resulted in high treatment well rate and shorter recovery duration.

The present study also has some limitations. First, the study represents a small study size with only 109 cases; second, it is a single institution study, thus the study population is limited; thirdly, we didn't use SF-36 score here to evaluate the treatment efficiency; and last, the present study only showed a short-term efficacy of the surgery, the long-term efficacy is not discussed. All

these limitations need further studies to give more clinical evidences.

In conclusion, we conducted a randomized controlled prospective study to investigate clinical efficacy of the transforaminal percutaneous endoscopic lumbar discectomy combined with ozone therapy for the treatment of lumbar disc herniation, and compared its short-term efficacy with fenestration discectomy. Results showed that the combination use of PELD and ozone treatment could significantly enhance the treatment efficacy and shorten the recovery duration of lumbar disc herniation patients, but didn't influence the incidence of postoperative complications.

REFERENCES

1. **Miwa S, Yokogawa A, Kobayashi T, Nishimura T, Igarashi K, Inatani H, Tsuchiya H.** Risk factors of recurrent lumbar disc herniation: a single center study and review of the literature. *J Spinal Disord Tech* 2015; 28(5):E265-269.
2. **Aizawa T, Ozawa H, Kusakabe T, Nakamura T, Sekiguchi A, Takahashi A, Sasaji T, Tokunaga S, Chiba T, Morozumi N, Koizumi Y, Itoi E.** Reoperation for recurrent lumbar disc herniation: a study over a 20-year period in a Japanese population. *J Orthop Sci* 2012; 17(2):107-113.
3. **Magalhaes FN, Dotta L, Sasse A, Teixeira MJ, Fonoff ET.** Ozone therapy as a treatment for low back pain secondary to herniated disc: a systematic review and meta-analysis of randomized controlled trials. *Pain Physician* 2012;15(2):E115.
4. **Apuzzo D, Giotti C, Pasqualetti P, Ferrazza P, Soldati P, Zucco GM.** An observational retrospective/horizontal study to compare oxygen-ozone therapy and/or global postural re-education in complicated chronic low back pain. *Functional Neurology* 2014; 29(1):1-9.
5. **Crockett MT, Moynagh M, Long N, Kilcoyne A, Dicker P, Synnott K, Eustace SJ.** Ozone-augmented percutaneous discectomy: A novel treatment option for refractory discogenic sciatica. *Clin Radiol* 2014;69(12):1280-1286.
6. **Ahn Y.** Transforaminal percutaneous endoscopic lumbar discectomy: technical tips to prevent complications. *Expert Rev Med Devices* 2012; 9(4):361-366.
7. **Ying J, Huang K, Zhu M, Zhou B, Yu W, Bi C, Teng H.** The effect and feasibility study of transforaminal percutaneous endoscopic lumbar discectomy via superior border of inferior pedicle approach for down-migrated intracanal disc herniations. *Medicine* 2016;95(8):e2899.
8. **Yao Y, Zhang H, Wu J, Liu H, Zhang Z, Tang Y, Zhou Y.** Minimally invasive transforaminal lumbar interbody fusion versus percutaneous endoscopic lumbar discectomy: revision surgery for the recurrent herniation after microendoscopic discectomy. *World Neurosurg* 2017; 99 (1): 89-95.
9. **Ozcan S, Muz A, Yildiz AA, Onal SA.** Intradiscal ozone therapy for lumbar disc herniation. *Cell Mol Biol Lett* 2018;64(5):52.
10. **Lehnert T, Naqib NN, Wutzler S, Nour-Eldin NE, Bauer RW, Kerl JM, Vogl TJ, Balzer JO.** Analysis of disk volume before and after CT-guided intradiscal and periganglionic ozone-oxygen injection for the treatment of lumbar disk herniation. *J Vasc Interv Radiol* 2012;23(11):1430-1436.
11. **Vanni D, Galzio R, Kazakova A, Pantalone A, Sparvieri A, Salini V, Magliani V.** Intraforaminal ozone therapy and particular side effects: preliminary results and early warning. *Acta Neurochir* 2016; 158(3):491-496.
12. **Ahn Y, Lee SH.** Postoperative spondylodiscitis following transforaminal percutaneous endoscopic lumbar discectomy: clinical characteristics and preventive strategies. *Br J Neurosurg* 2012; 26(4):482-486.
13. **Tacconi L, Baldo S, Merci G, Serra G.** Transforaminal percutaneous endoscopic lumbar discectomy: outcome and complications in 270 cases. *J Neurosurg Sci* 2018.
14. **Sangwan S, Kundu Z, Raj S, Kamboj P.** Lumbar disc excision through fenestration. *Indian J Orthop* 2006;40(2):86-89.
15. **Lavyne MH.** Pars interarticularis fenestration in the treatment of foraminal disc herniation: a further surgical approach. *Neurosurgery* 1998; 42(1):89-90.
16. **Lee HJ, Kim JS, Ryu KS.** Transforaminal percutaneous endoscopic lumbar discectomy with percutaneous epidural neuroplasty

- in lumbar disc herniation: technical note. *World Neurosurg* 2017; 98:876.e23-.e31.
17. **Yong A, Lee SH, Lee JH, Jin UK, Wei CL.** Transforaminal percutaneous endoscopic lumbar discectomy for upper lumbar disc herniation: clinical outcome, prognostic factors, and technical consideration. *Acta Neurochir* 2009; 151(3):199-206.
 18. **Zheng C, Wu F, Lin C.** Transforaminal percutaneous endoscopic discectomy in the treatment of far-lateral lumbar disc herniations in children. *Int Orthop* 2016; 40(6):1099-1102.
 19. **Kim CH, Chung CK, Woo JW.** Surgical Outcome of Percutaneous Endoscopic Interlaminar Lumbar Discectomy for Highly Migrated Disc Herniation. *Clin Spine Surg* 2016; 29(5):E259-266.
 20. **Ding W, Yin J, Yan T, Nong L, Xu N.** Meta-analysis of percutaneous transforaminal endoscopic discectomy vs. fenestration discectomy in the treatment of lumbar disc herniation. *Orthopade* 2018(17):1-11.
 21. **Paoloni M, Di SL, Cacchio A, Apuzzo D, Marotta S, Razzano M, Franzini M, Santilli V.** Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation: a multicenter, randomized, double-blind, clinical trial of active and simulated lumbar paravertebral injection. *Spine* 2009; 34(13):1337-1344.
 22. **Muto M, Giurazza F, Silva RP, Guarnieri G.** Rational approach, technique and selection criteria treating lumbar disk herniations by oxygen-ozone therapy. *Interv Neuroradiol* 2016; 22(6):736-740.
 23. **Gautam S, Rastogi V, Jain A, Singh AP.** Comparative evaluation of oxygen-ozone therapy and combined use of oxygen-ozone therapy with percutaneous intradiscal radiofrequency thermocoagulation for the treatment of lumbar disc herniation. *Pain Pract* 2015; 11(2):160-166.