Int J Clin Exp Med 2015;8(1):526-532
www.ijcem.com /ISSN:1940-5901/IJCEM0002928

Original Article

Target radiofrequency combined with collagenase chemonucleolysis in the treatment of lumbar intervertebral disc herniation

Daying Zhang[1], Yong Zhang[1], Zhijian Wang[1], Xuexue Zhang[1], Mulan Sheng[2]

[1]Department of Pain, The First Affiliated Hospital of Nanchang University, Nanchang 330006, China; [2]Department of Pain, The Third Hospital of Nanchang, Nanchang 330009, Jiangxi Province, China

Received October 2, 2014; Accepted December 8, 2014; Epub January 15, 2015; Published January 30, 2015

Abstract: Both target radiofrequency thermocoagulation and collagenase chemonucleolysis are effective micro-invasive therapy means for lumbar intervertebral disc herniation. In order to analyze the clinical effects of target radiofrequency thermocoagulation combined with collagenase chemonucleolysis on lumbar intervertebral disc herniation, the contents of hydroxyproline and glycosaminoglycan were measured and the histological changes of nucleus pulposus was detected in the vitro experiments. Radiofrequency thermocoagulation reduced the hydrolyzation of herniated nucleus pulposus caused by collagenase, as well as the content of hydroxyproline and glycosaminoglycan. Furthermore, 236 patients with lumbar intervertebral disc herniation were treated by target radiofrequency thermocoagulation combined with collagenase chemonucleolysis. The efficiency was evaluated according to Macnab criteria, and the index of lumbar disc herniation (IDH) was compared pre-operation with 3 months post-operation. The post-operative good rate was 66.5% (157/236) at 2 weeks post-operation, and 88.1% (208/236) at 3 months post-operation. In the post-operative follow-up exam, 86.8% of the re-examined cases demonstrated smaller or ablated protrusion, with reduced IDH values from pre-operation, which was statistically significant. No serious complications were detected intra-operatively and post-operatively. In conclusion, target radiofrequency combined with collagenase chemonucleolysis was an effective and safe method for treatment of lumbar intervertebral disc herniation.

Keywords: Lumbar intervertebral disc herniation, radiofrequency, collagenase chemonucleolysis

Introduction

The lumbar intervertebral disc is a complex structure composed of collagen, proteoglycans, and sparse fibrochondrocytic cells which serve to distribute forces exerted on the spine [1]. When the anterior side of the disc is compressed while sitting or bending forward to lift weights, the nucleus pulposus may press the annulus fibrosis on the posterior side of the disc. Continuous stretching of the annulus fibrosis and increased internal pressure (200 to 300 psi) results in the tear and rupture of the confining membrane. Then the nucleus pulposus herniated into the spinal canal, forming lumbar disc herniation and pressing against the spinal nerves, thus producing intense and usually disabling pain [2].

The lumbar intervertebral disc herniation, often occurring in the lower back between the fourth and fifth lumbar vertebra or between the fifth and the sacrum, is the common clinical cause of low back and leg pain. Patients suffering from lumbar disc herniation show symptoms affecting the lower back, buttocks, thigh, anal/genital region, and may radiate into the foot and/or toe. Lumbar disc herniation is a commonly seen in young and middle-aged patients [3]. The majority of spinal disc herniation cases occur in lumbar region (95% in L4-L5 or L5-S1). The second most common site is the cervical region (C5-C6, C6-C7). The thoracic region accounts for only 0.15% to 4.0% of cases. The economic impact of various disc related disorders, back pain, and/or radiculopathy is in terms of days lost to work and reduced productivity. According to a recent estimate, USA spends an estimated 100 billion dollars per year [4] attempting to treat the disorders related to lumbar disc herniation.

There are lots of surgical and nonsurgical treatment procedures for lumbar disc herniation. The micro-invasive therapy means of lumbar intervertebral disc herniation which have been increasingly accepted in patients includes plasma radiofrequency ablation, laser gasification decompression, collagenase chemonucleolysis, radiofrequency ablation, cutting aspiration, and intervertebral foramen arthroscopic treatment. These clinical technologies have corresponding indications and limitations. Therefore, how to choose appropriate method and period often confuses the clinicians.

Chemonucleolysis (CN) was described by Smith in 1963 [5, 6] and the drug chymodiactin was approved for use by the US Food and Drug Administration (FDA) in 1982 [7]. Collagenase chemonucleolysis is an effective treatment method for lumbar intervertebral disc herniation which has been used clinically for more than 30 years. The intradiscal, intervertebral and combination of the two injections has been reported both here and abroad with good rates between 81.09%-90.58% [8]. Collagen hydrolysis makes the protrusion smaller or disappeared, relieving or resolving the compression of nerve root by the protrusion. Collagenase could also inhibit some inflammatory mediators and relieve inflammation of nerve root and peripheral tissues. However, the increased in tradiscal and canalis spinal pressure during the collagenase chemolysis may result in serious complications such as worse nerve root compression, aggravated leg pain, and even nerve root damage [9]. Zhang reported that the injection of collagenase caused damage to the nerve root with a frequency of 0.48%. The post-operation pressure may increase and damage the nerve root for the patients with secondary canal stenosis.

Radiofrequency thermocoagulation (RF) is another effective treatment method for lumbar intervertebral disc herniation. Radiofrequency treatment can cause nucleus pulposus pyknosis during lumbar intervertebral disc herniation, repair annulus or destruct hyperplasia migration of nerve endings within the annulus and then change internal environment of lumbar intervertebral disc. The treatment area of radiofrequency (RF) is a circle of RF damage radius of 5 mm, with the working end of RF electrode as the zero point. The classical recommended indication was bulging protrusion, and the short-term effect was poor, the long-term effect was poor associated with imaging changes [10]. Radiofrequency thermocoagulation causes the focal pyknotic nucleus pulposus, decreases in tradisccal pressure [11, 12], and mediates the internal environment of intervertebral disc through inhibiting the release of inflammatory mediators. Therefore, radiofrequency thermocoagulation was used clinically as one of the approaches to treating discogenic pain. The efficiency of clinical applications in protruded and prolapsed lumbar intervertebral disc herniation was not satisfactory. There are risks of nerve root damage for treating protrusion target.

How to avoid aggravating nerve compression caused by collagenase injection of perioperative hypertension in lumbar disc is a valuable research topic. RF may decrease the pressure caused by nucleus pulposus dissolving during collagenase chemonucleolysis through reducing the nucleus pulposus which is the substrate of collagenase. The nucleus pulposus prolapsed from spinal canal during the RF treatment can be dissolved through collagenase chemonucleolysis. Therefore, the treatment procedure combining target radiofrequency thermocoagulation with collagenase chemonucleolysis may improve the safety and efficiency of microinvasive technologies for the treatment of lumbar intervertebral disc herniation.

In this paper, we present the results of an in vivo and in vitro study of treatment efficiency for lumbar intervertebral disc herniation through combining target radiofrequency thermocoagulation with collagenase chemonucleolysis. The purpose of this study was to improve the efficiency & safety, and extend the indications of microinvasive technologies. The effect of radiofrequency thermocoagulation on the porcine intervertebral disc specimen and the human nucleus pulposus tissue specimen treated by collagenase chemonucleolysis was detected in vitro experiment. Furthermore, 236 patients were treated through radiofrequency thermocoagulation combined with collagenase chemonucleolysis and the treatment efficiency was analyzed.

Materials and methods

General materials

One fresh porcine lumbar spine specimen containing four complete intervertebral discs was used for detecting the effect of target radiofrequency thermocoagulation.

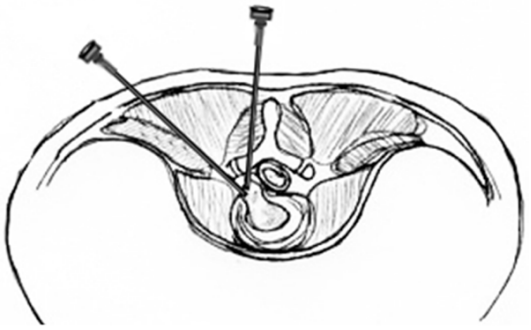

Figure 1. Puncture approach of lumbar facet joints and safe triangular region of intervertebral foramen.

In order to analyze the effect of radiofrequency thermocoagulation on the human nucleus pulposus tissue specimen treated by collagenase chemonucleolysis in vitro experiment, 24 nucleus pulposus tissue specimens obtained from nucleus pulposus resection decompression operation. 236 patients (144 males and 92 females), the average age of them was 37.2 years were treated by radiofrequency thermocoagulation combined with collagenase chemonucleolysis. The case inclusion criteria is clear lower extremity radicular pain symptoms which is consist with CT and MRI imaging, single gap intervertebral disc prolapse, and secondary spinal or lateral recess stenosis. The patients containing 4 L34, 146 L45, and 86 L5S1 cases, were unilateral or central unilateral herniation. There were no contraindications for micro-invasive surgery of lumbar intervertebral disc in this group, in which collagenase chemolysis for lumbar intervertebral disc herniation was the indication [13].

The vitro procedure

RF puncture needle with 2 mm and 5 mm working end was used to conduct anterior puncture through the central portion in two porcine intervertebral disc segments. The standard RF was performed with the temperature of 90°C and working time of 90 s. The exposed nucleus pulposus along the annulus fibrosis was separated with a knife slice after RF. Meanwhile, the adjunct intervertebral disc without RF treatment was also separated and used as control.

The 24 tissue specimens were randomly divided into 4 groups (n=6): RF group (group I, RF parameter: 90°C, 240 s), Collagenase group (group II, Collagenase injection quantity 100 U/0.3 ml), radiofrequency thermocoagulation combined with Collagenase group (group III, Collagenase is injected when the temperature reduced to blew 40°C after radiofrequency treatment. The parameters of RF and the dosage of collagenase are the same with group I and II. Group IV is the blank control. 1 g of one-piece nucleus pulposus tissue was used in each group. 12 h later, the value of hydroxyproline and glycosaminoglycan were measured by the spectrophotometer and the precipitate was histopathologically examined after immobilized.

Standardized preoperative preparation

Responsible discs were defined and the indications were strictly controlled. The patients were generally prepared and trained to relieve the bowels on bed. Operation informed consent forms were signed and the patients must relieve themselves before operation.

Video surveillance puncture

The appropriate puncture pathway (as shown in **Figure 1**) including lumbar facet joints and safe triangular region of intervertebral foramen was designed according to projections morphology and the anatomical characteristics of lumbar spine [14] detected by patients' diagnostic imaging data (X-Ray, CT, MRI). Puncture point was marked and the direction and angle of point were conducted through the video surveillance.

Radiofrequency and the injection method of collagenase

Appropriate RF electrodes with different working ends were chose to ensure the working end could completely insert into the protrusions after the puncture needle reached the protrusions.

When the puncture reaches target anatomical site, inject the contrast agent 0.3-0.5 mL and observe the diffusion pattern, duplicate the protrusion imaging as clear as possible. If the contrast agent diffused more than 7 mm away from electrode zero point, collagenase of 75-200 U/0.3-0.5 ml could be injected. Measure the electrical impedance (the electrical impedance of nucleus pulposus is generally 200-400 Ω) after the RF electrode is placed, then measure the sensory evoked impedance (100 HZ, 0.5-1.0 mA) and motion evoked impedance (3 HZ, 1.0-2.0 mA). The failure of inducing pain

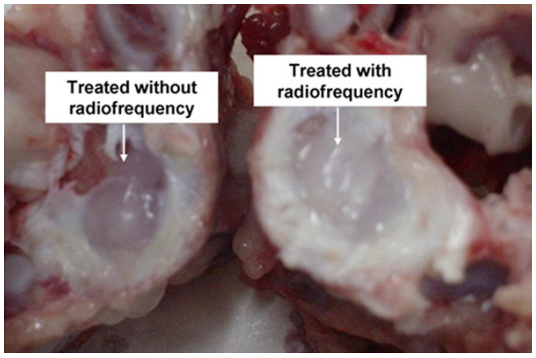

Figure 2. Porcine intervertebral disc specimen before and after RF.

and lower limb muscle contraction indicated that the electrode is far from the nerve root. Set the initial working parameter at 70°C, 60 s to conduct single consecutive radiofrequency thermocoagulation, and then increase the parameter to 80°C, 60 s, 85°C, 60 s, 90°C, 60 s stepwise. Now the lumbar & leg pain and warm sensation could be duplicated, but electric shock-like numbness or pain should be avoided, reconfirming that the electrode is localized at the target and far away nerve root. Set the parameter at 95°C, 90 s and work for two cycles. During the whole radiofrequency thermocoagulation, keep communicating with the patients, pay close attention to the status of patient pain, and check the nerve function of lower extremity. If the collagenase has not been pre-injected, unplug the RF electrode when the temperature of electrode working end decreased to about 40°C after RF termination. The contrast agent (ioversol) 0.3-0.5 ml was injected and the diffusion of contrast agent into protrusion shall be observed. Then inject collagenase 75-200 U/0.3-0.5 ml slowly.

Postoperative management

The patients were taken back to the hospital ward after operation and administrated with antibiotics for 3 days. After lying on bed conventionally for 7-10 days, the patients could get up with a waist band. Appropriate back muscle exercise should be performed and the manual labor must be prohibited within 3 months.

Efficiency evaluation

The efficiency was evaluated according to Macnab criteria [15, 16] 2 weeks and 3 months after surgery (Excellent: The pain symptom disappeared without limited motion function and the normal work and activities were recovered. Good: The pain occasionally existed and most of the pre-existing symptoms resolved. The patients could perform mild manual work. Fair: Part of the symptoms resolved. The patients still suffered from pain and could not work normally. Poor: The symptoms of nerve root compression still appear and the patients need further therapy). Measure and compare the index of vertebral disc herniation (IDH) before and after operation, ie, sagittal diameter × diameter for protruding disc/sagittal diameter × diameter for spinal canal. Statistical analysis was tested by paired sample T-test.

Results and discussion

Effect of radiofrequency thermocoagulation on nucleus pulposus

The porcine intervertebral disc specimen was treated by radiofrequency thermocoagulation to detect the effectiveness of RF. As shown in **Figure 2**, the boundary of intervertebral disc nucleus pulposus and annulus fibrosis was distinct and the nucleus pulposus was clear without RF treated. After treated by RF, the boundary of intervertebral disc nucleus pulposus and annulus fibrosus became unclear and the nucleus pulposus showed milk white. The turbidity of nucleus pulposus in intervertebral disc treated with RF indicated that RF could deform the nucleus pulposus, reduce the total amount of nucleus pulposus collagen fibrils which was the lysate substrate of collagenase, and decrease the pressure caused by the nucleus pulposus collagen fibrils procedure.

Effect of radiofrequency thermocoagulation on collagenase chemonucleolysis in vitro studies

Collagenase chemonucleolysis may increase the pressure in the lumbar disc and aggravate nerve compression, which is the main risk of collagenase chemonucleolysis. The porcine intervertebral disc specimen treated by RF (**Figure 2**) indicated that RF may relieve the nerve compression through reducing the total amount of nucleus pulposus collagen fibrils and offset the risk of collagenase chemonucleolysis. In order to further verify this speculation, 24 nucleus pulposus tissue specimens were obtained and randomly divided into 4 groups as described in

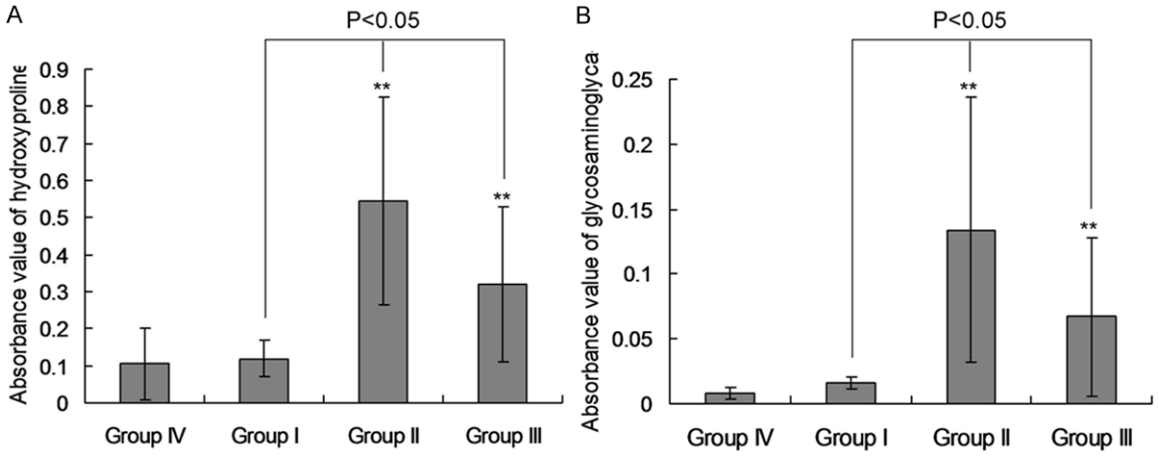

Figure 3. The absorbance value of hydroxyproline (A) and glycosaminoglycan (B) of Group I, II, III and IV.

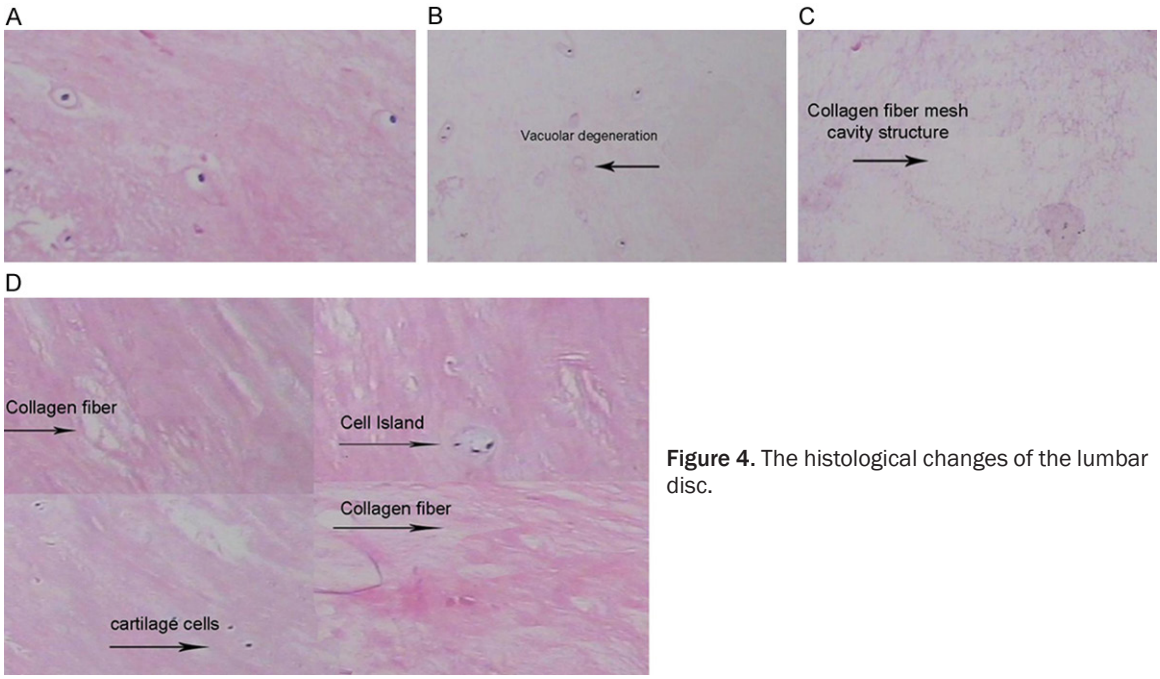

Figure 4. The histological changes of the lumbar disc.

Table 1. Comparison of efficiency at various time post-operatively

Post-operative time	Excellent	Good	Fair	Poor	Good rate
2 weeks	45	112	53	26	66.5%
3 months	118	90	22	6	88.1%

Materials and methods: RF group, Collagenase group, Radiofrequency thermocoagulation combined with Collagenase group, and the blank control group. 12 h after treated, the content of hydroxyprolineand glycosaminoglycan were measured by the spectrophotometer and the precipitate was histopathologically examined.

The absorbance value of hydroxyproline of Group I, II, III and IV was 0.096±0.021, 0.549±0.021, 0.314±0.112, and 0.087±0.040 respectively (**Figure 3A**). The absorbance values of group II and III were significantly higher than that of group IV ($P < 0.001$). When compared in pairs among group I, II, and III, the differences were statistically significant ($P < 0.01$). However, the difference between group I and IV have no statistical significance (P=0.86).

The content of glycosaminoglycan was also detected. As shown in **Fiugre 3B**, the absor-

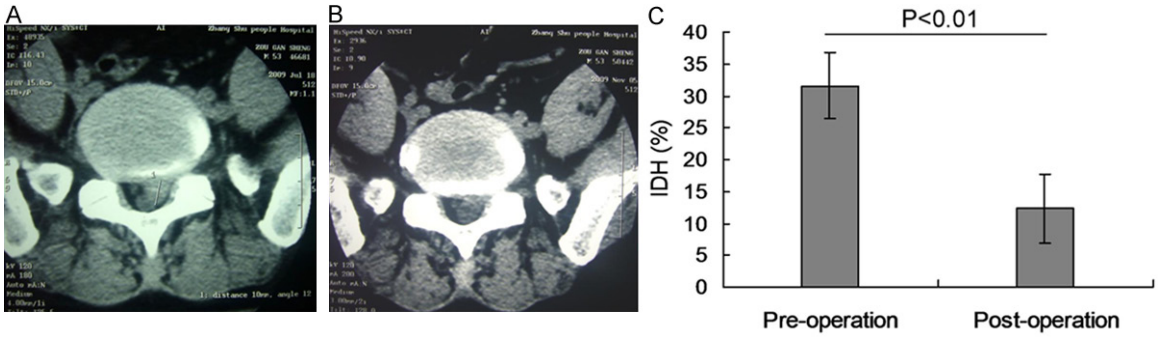

Figure 5. Pre-operation and post-operation results. A. Pre-operation CT indicated obvious herniated disk. B. Post-operation re-exam demonstrates smaller protrusion. C. Comparison of pre-operation and post-operation IDH ($P < 0.01$).

bance value of glycosaminoglycan of Group I, II, III and IV was 0.012±0.002, 0.13±0.051, 0.054±0.025, and 0.006±0.002 respectively. The absorbance values of group II and III were significantly higher than that of group IV ($P < 0.001$). When compared in pairs among group I, II, and III, the differences were statistically significant ($P < 0.05$). However, the difference between group I and IV have no statistical significance ($P=0.74$).

The histological changes of the lumbar disc were further analyzed. Vacuole degeneration was detected in the nucleus pulposus of group I (**Figure 4A**). Collagen contracted and its orientation had no obvious changes. Group II: Collagenous fiber in nucleus pulposus has almost been dissolved by collagenase, leaving only fiber mesh cavity structure (**Figure 4B**). Group III: The number of nucleus pulposus cells reduced. Nucleus pulposus deformed and the cell spacing became larger. Meanwhile, vacuoles degeneration became obviously and collagenous fiber was arranged randomly and loosely (**Figure 4C**). Group IV: Collagen fibres mesh became loose and appeared to be wavy, fusiformis or taper. Non-uniform collagenous fiber was formed and organized mesh could not be observed. Condorcet spread between collagenous fiber and cell islands formed by multiple chondrocytes can be observed (**Figure 4D**).

Collagenase can dissolve collagen fibers and degrade the proteoglycan in intervertebral disc. Radiofrequency thermocoagulation makes the intervertebral disc nucleus become “solidification and shrinkage” and subsequently the collagen contracted. Radiofrequency thermocoagulation reduced the hydrolyzation of herniated nucleus pulposus caused by collagenase, as well as the degradation of proteoglycan content in nucleus pulposus. These results suggested that target radiofrequency combined with collagenase chemonucleolysis should be an effective and safe treatment means for the lumbar intervertebral disc herniation.

Treatment efficiency of radiofrequency thermocoagulation combined with collagenase chemonucleolysis

Considering the advantage of the treatment means of radiofrequency thermocoagulation combined with collagenase chemonucleolysis, 236 patients were treated with this method. The comparison of efficiency in this group was presented in **Table 1**. The good rate was 66.5% (157/236) two weeks after operation, 88.1% (208/236) three months after operation.

197 patients were re-examined by CT three months after operation, of which 171 cases with smaller or disappeared protrusions (**Figure 5A**, **5B**), accounting 86.8% of all re-examined cases. The comparison between pre-operation and post-operation was presented in **Figure 5C**, the post-operation IDH was obviously smaller than pre-operation with a statistical difference. There were no complications such as psoas hematoma, infection, or nerve injury in 236 patients who had receivedtarget radiofrequency combined with collagenase chemonucleolysis.

Target radiofrequency thermocoagulation denatured the nucleus pulposus of porcine intervertebral disc specimen and reduced the total amount of nucleus pulposus collagen fibrils. Further vitro experiments confirmed that target radiofrequency thermocoagulation reduced the

content of hydroxyproline and glycosaminoglycan which released from nucleus pulposus during collagenase chemonucleolysis. These results indicated that RF could avoid the rising pressure resulting from collagenase chemonucleolysis. In addition, 236 patients were treated by radiofrequency thermocoagulation combined with collagenase chemonucleolysis to detect its treatment efficiency. The post-operation IDH was significantly smaller than pre-operation and no complications were detected. Taken together, targerradiofrequency thermocoagulation combined with collagenase chemonucleolysis would be an effective and safe micro-invasive therapy means for lumbar intervertebral disc herniation.

Disclosure of conflict of interest

None.

Address correspondence to: Mulan Sheng, Department of Pain, The Third Hospital of Nanchang, Zhan Qian West Road, No. 240, Nanchang 330009, Jiangxi Province, China. Tel: +86-0791-86615534; Fax: +860791-86615534; E-mail: ncmulansheng@yeah.net

References

[1] Yuan C, Zhu H, Song D, Wei W, Zhu R, Mei X, Zou J, Yang H. Impact and clinical significance of pedicle length on spinal canal and intervertebral foramen area. Int J Clin Exp Med 2014; 7: 163-169.

[2] Vijaya KV. Lumbar Disc Herniation. Orthopedic & Muscular System 2012; 1: e101.

[3] Kermani HR, Keykhosravi E, Mirkazemi M, Ehsaei MR. The relationship between morphology of lumbar disc herniation and MRI changes in adjacent vertebral bodies. Arch Bone Jt Surg 2013; 1: 81-85.

[4] Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. J Bone Joint Surg Am 2006; 88: 21-24.

[5] Smith L. Enzyme dissolution of nucleus pulposus. Nature 1963; 4887: 1311-1312.

[6] Smith L. Enzyme dissolution of the nucleus pulposus in humans. JAMA 1964; 187: 137-140.

[7] Javid MJ. Chemonucleolysis vs laminectomy: a cohort comparison of effectiveness and changes. Spine 1995; 20: 2016-2022.

[8] Han HJ, Kim JY, Jang HY, Lee B, Yoon JH, Jang SK, Choi SH, Jeong SW. Fluoroscopic-guided intradiscal oxygen-ozone injection therapy for thoracolumbar intervertebral disc hemiations in dogs. In Vivo 2007; 21: 609-613.

[9] Zhang DY. The prevention of adverse events associated with collagenase chemolysis for the treatment of lumbar intervertebral disc herniation. Chinese J Pain Med 2007; 13: 380.

[10] Li M, Chen Y, Luo Z, Zhang W, He B. Experimenta observation of vitro pigs' heart with bipolar radiofrequency ablation. Int J Clin Exp Med 2013; 6: 614-620.

[11] Troussier B, Lebas JF, Chirossel JP, Peoc'h M, Grand S, Leviel JL, Phelip X. Percutaneous intradiscal radiofrequency thermocoagulation. Acadaveric study. Spine 1995; 20: 1713-1718.

[12] Podhajsky RJ, Belous A, Johnson K, Maul DH, Finch PM. Effects of monopolar radiofrequency heating on intradiscal pressure in sheep. Spine J 2007; 7: 229-234.

[13] Zhang DY. Considerations of collagenase chemolysis for the treatment of lumbar intervertebral disc herniation. ChinJ Pain Med 2006; 12: 64.

[14] Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. J Bone Joint Surg Am 2006; 88: 21-24.

[15] Macnab I. Negative disc exploration:an analysis of the causes of nerve root involvement in 68 patients. J Bone Joint Surg 1971; 53: 891-903.

[16] Zheng JW, Wang L, Zhou Q, Mai HM, Wang YA, Fan XD, Qin ZP, Wang XK, Zhao YF. A practical guide to treatment of infantile hemangiomas of the head and neck. Int J Clin Exp Med 2013; 6: 851-860.