European Journal of Radiology xxx (2008) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Percutaneous treatment of non-contained lumbar disc herniation by injection of oxygen–ozone combined with collagenase

ZhiQun Wu[a,*], Long Xiao Wei[a,1], Jun Li[b], Yiqing Wang[a], DaiHui Ni[a], Peng Yang[c], Yuhai Zhang[c]

[a] Therapy Center of Pain, Division of Interventional Radiology, Tang Du Hospital, The Fourth Military Medical University, Xian 710038, China
[b] Therapy Center of Pain, Division of Orthopedic Surgery, Tang Du Hospital, The Fourth Military Medical University, Xian 710038, China
[c] Department of Biostatistics, The Fourth Military Medical University, Xian 710032, China

ARTICLE INFO

Article history:
Received 31 March 2008
Accepted 28 July 2008

Keywords:
Chemonucleolysis
Collagenase
Oxygen–ozone
Surgery
Lumbar disc herniation

ABSTRACT

Purpose: To evaluate the therapeutic results of oxygen–ozone combined collagenase injection for the treatment of lumbar disc herniation compared to the surgery. And to explore the role of this minimally invasive treatment as an alternative to disc surgery.
Materials and methods: Two groups of patients ($n = 108$) were treated with different ways respectively. Minimally invasive group of patients was treated with the injection of oxygen–ozone combined with collagenase into the lumbar disc or the epidural space; the other group was treated with traditional surgery. After the treatment, the patients were followed-up and the therapeutic effect was assessed at 2 weeks, 3 and 12 months by the modified Macnab criteria.
Results: The success rate was 86.11% and 88.89% in minimally invasive group at 3 and 12 months respectively, while 92.59% and 95.37% in surgical group. There was no statistically significant difference between two groups at 3 and 12 months ($P = 0.123$, $P = 0.08$). However, the surgical group produced a statistically significant greater improvement for back pain and disability in the first few weeks ($P = 0.0001$). The success rate was 51.86% and 85.18% at 2 weeks in minimally invasive group and surgical group respectively. No serious complication occurred in this group.
Conclusions: The combination of the oxygen–ozone with collagenase shows significant reductions in pain and improvements in function at 3 and 12 months, it can be considered as an option for the treatment of non-contained lumbar disc herniation instead of surgery.

1. Introduction

The lumbar disc herniation was one of the most common disease and most frequent cause of absence from work. The therapy of lumbar disc herniation includes conservative treatment, surgery and minimally invasive techniques. Conservative treatment was only suitable for the patients with very light clinical symptoms and signs [1]. The surgery was effective but with more trauma and complications [2]. Currently, a number of minimally invasive techniques have been described [3]. These techniques include: chemonucleolysis [4–7], percutaneous manual nucleotomy [8], percutaneous laser disc decompression (PLDD) [9], intradiscal electrothermy [10]. These procedures have reported success rates of 70%–75%, but each has its limitations [11].

Chemonucleolysis is a technique that involves the percutaneous puncture of a needle intradisc or extradisc to shrink or remove the herniation with chemical materials. The clinical studies of chemonucleolysis showed that these procedures improved the clinical outcomes [4–7], but the role of chemonucleolysis as an alternative to disc surgery is still disputed. Especially the chemonucleolysis with chemopapaine resulted in an unacceptable level of complications and is no longer available in the United States [11]. Although no serious complications related to the chemonucleolysis with collagenase have been reported so far, however, the success rate of this procedure was still unsatisfied. Recently, chemonucleolysis with the oxygen–ozone also has been reported to improve the signs and symptoms of patients with non-contained lumbar disc herniations [4], but the success rates of this procedure was unsatisfied too. The purpose of this study was to explore if the combination of collagenase and oxygen–ozone can improve the success rate of chemonucleolysis for the treatment of non-contained lumbar disc herniations, and this study was also to determine if the chemonucleolysis with the combination of collagenase and oxygen–ozone can be considered as an alternative to disc surgery.

* Corresponding author. Tel.: +86 29 83377864; fax: +86 29 83546646.
E-mail address: zhiqunwu@yahoo.com (Z. Wu).
[1] Co-first author.

0720-048X/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejrad.2008.07.029

Table 1
Patient's characteristics

Patient's characteristics	Group A (non-surgical)	Group B (surgical)	Statistical analysis
Number of patients	108	108	
Gender			
Male	58	65	$\chi^2 = 0.925$,
Female	50	43	$P = 0.336$
Age (yrs)			
Range	46.5 ± 1.85	46.2 ± 1.29	$t = 1.382$,
Range	22–68	25–65	$P = 0.168$
Mode of onset of pain			
Work related	15% (16)	21% (23)	$\chi^2 = 2.716$,
Trauma	13% (14)	18% (19)	$P = 0.257$
Other	72% (78)	61% (66)	
Duration of pain (months)			
Range	1–5	1–5	$Z = -1.056$,
<1	45% (49)	52% (56)	$P = 0.291$
1–4	43% (46)	39% (42)	
>4	12% (13)	9% (10)	
Pain ratio			
Back pain only	8% (9)	12% (13)	$Z = -0.897$,
Back worse than leg	47% (51)	45% (49)	$P = 0.370$
Back and leg pain equal	28% (30)	33% (36)	
Leg worse than back	17% (18)	10% (10)	
Straight-leg-raising tests			
Positive	92% (99)	88% (95)	$\chi^2 = 0.889$,
Negative	8% (9)	12% (13)	$P = 0.346$
Decompression sites			
L3–4	16% (17)	15% (16)	$Z = -0.690$,
L4–5	61% (66)	57% (62)	$P = 0.490$
L5–S1	23% (25)	28% (30)	

Two groups have no statistical difference.
The table showed the data of all patients and the statistical analysis result.

2. Materials and methods

The study was conducted at a large therapy center of pain, and was approved by the University's Institutional Review Board. The Injection of Collengenase was bought from the Shanhai Qianyuan Medical Company. The ozone device was bought from Herrmann Apparatebau Gmbh, German.

2.1. Inclusion criteria

Patient's age arranged from 20 to 70; low back pain with one or two leg pain; evidence of discogenic disease on CT or Magnetic Resonance Imaging (MRI) scan indicating the single level non-contained herniation; failure of non-surgical therapies in the prior 6 months, including physical therapy, non-steroidal anti-inflammatory medicines, epidural steroidal treatment.

2.2. Exclusion criteria

Unstable neurological deficits and cauda equina syndrome; stenosis of vertebral canal; protrusion calcification; dislocation of vertebrate; lateral access stenosis; mental disorder; malignancy; other chronic diseases.

2.3. Randomization procedure

216 patients during the study period (January 2003–November 2005) in the therapy center of pain were involved in this trial. Table 1 was the clinical materials of the two groups of patients. All patients meet the inclusion and exclusion criteria, and all the patients signed the paper of agreement for the treatment. During the first visit to the outpatient clinic of the therapy center of pain, the patient's history and a standard neurological examination will be documented. Conform our selection criteria, the neurosurgeon decides whether a patient is eligible for this trial. The study will be explained to the patient, and after the patients signed the paper of agreement for the treatment, the patients were admitted to the therapy center of the pain. Then the questionnaires are filled according to the modified Macnab criteria [12] (Table 2).

Patients will be randomly allocated to either minimal invasive group (group A) or conventional discectomy (group B). Randomization will take place in the admitting room by the research nurse. The research nurse allocated the patients according to the random numbers formed by the computer to ensure equal distribution of the randomization treatments. The data manager at the department of biostatistics, who is not involved in the selection and allocation of patients, will prepare coded, sealed envelopes containing the treat-

Table 2
Macnab criteria for assessing clinical outcome after treatment

Outcome	Description
Excellent	Disappearance of symptoms. Complete recovery in working and sports activities.
Good	Occasional episodes of low back pain or sciatica. No limitations of Occupational activities.
Fair	Insufficient improvement of symptoms. Periodical administration of drugs.
Poor	No improvement of clinical situation. Limitation of physical activities.

The criteria of "excellent, good, fair and poor" for assessing clinical outcome after treatment were showed.

Please cite this article in press as: Wu Z, et al. Percutaneous treatment of non-contained lumbar disc herniation by injection of oxygen–ozone combined with collagenase. Eur J Radiol (2008), doi:10.1016/j.ejrad.2008.07.029

ment allocation. The treatment were carried out by two specialists who are blind to the study, one is responsible for the minimal invasive procedure, the other is responsible for the conventional open surgery, and they are not allowed to participate the assessment of the results. In the operating room, the surgeon will open the envelope and the allocated treatment is performed. Research nurses are kept blinded for the allocated treatment during the follow-up period of 1 year.

After the treatment, doctor Wang and Wei, who were blinded with the treatment, will call the patients at 2 weeks, 3 and 12 months respectively and the therapeutic effect (leg pain, back pain and self-reported disability) was assessed according to the modified Macnab criteria [12] (Table 2), and the main questionnaire will be filled and sent to the data center.

Dr. Peng Yang, who is an assistant professor in the department of biostatistics and blinded to the treatment too, carried out the statistical analysis. The statistical methods used include Chi-square test, *t* test and Wilcoxon rank sum test.

2.4. Chemonucleolysis technique

A standardized chemonucleolysis technique was performed, and C-arm fluoroscopy was used for the procedures and anteroposterior and lateral spot films were obtained for documentation purposes.

In non-germ surgical operation room, the patient lies on the surgical operation bed facing down with a cushion under the lower abdomen. The treatment level was localized and local anesthesia was applied to the skin 6–8 cm lateral to the midline. The 22-gauge needle was directed toward the center of the disc under fluoroscopic guidance, and the annulus was punctured (Figs. 1 and 2). After the needle was determined radiographically to be in the appropriate position, inject 35–45 ug/ml of 10–15 ml O2–O3 into the disc very slowly, then pull out the needle waiting for 20 min, then let the patient lie down on the pain-side, and puncture the needle to the epidural space through intervertebral foramen, the needle point should lie to the 1/3 and 2/3 intersection level of intervertebral foramen in lateral view, and lie to the inner margin of pedicle of vertebral arch in anteroposterior view (Figs. 3 and 4). After the needle was determined radiographically to be in the appropriate position, 0.5–1 ml of non-ionic contrast material (Omnipaque300) was injected to document appropriate contrast spread into the epidural space without intravascular uptake and not inside the spinal dura mater (Figs. 3 and 4), then injected the collagenase 1200 u (4 ml) into the protrusion area inside the epidural space very slowly (10 min). Pull out the needle and let the patients keep an anteroposterior position (30–45 angle to the bed) for 6–8 h to prevent the collagenase diffuse to other place.

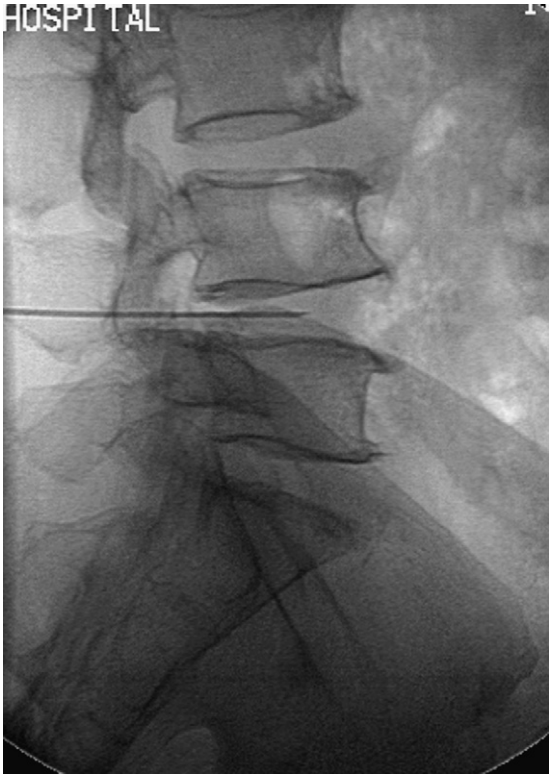

Fig. 1. The lateral position of the needle. The lateral position of the needlepoint after the intradisc acupuncture was showed.

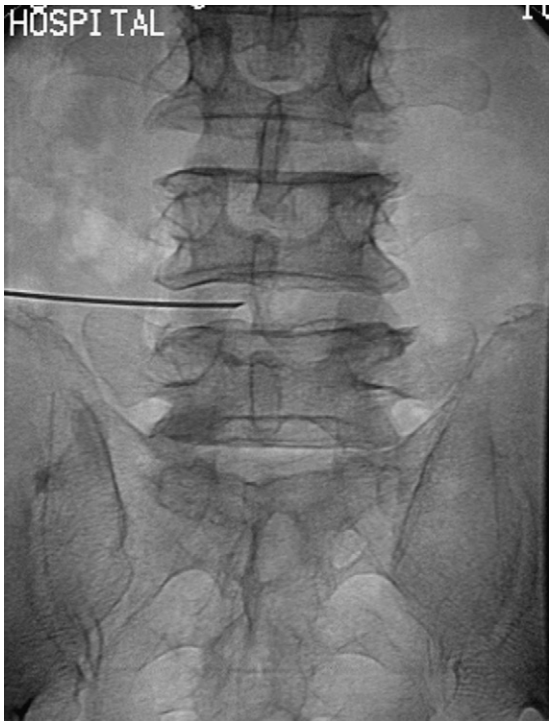

Fig. 2. The anteroposterior position of the needle. The anteroposterior position of the needlepoint after the intradisc puncture was showed.

After the operation, patients should take antibiotics orally and infused 20% mannitol 250 ml, dexamethasone 5 mg and citicoline sodium injection 0.5 g through venous way for 3 days, or gave some painkiller if necessary. The patients were followed-up for 12 months.

2.5. Discectomy

The patients were treated with traditional discectomy. Blocking the posterior branches of spinal nerves by local anesthesia, discectomy was performed to remove the nucleus pulposus by lateral and interlamina access.

3. Results

The therapeutic effect (leg pain, back pain and self-reported disability) was assessed at 2 weeks, 3 and 12 months by the modified Macnab criteria [12] (Table 2).

A satisfactory therapeutic outcome was obtained in both groups at 3 and 12 months. In group A, treatment was a success (excellent

Please cite this article in press as: Wu Z, et al. Percutaneous treatment of non-contained lumbar disc herniation by injection of oxygen–ozone combined with collagenase. Eur J Radiol (2008), doi:10.1016/j.ejrad.2008.07.029

Table 3
The outcomes of two groups after the treatment

Outcome	Group A (non-surgical, $n = 108$)			Group B (Surgical, $n = 108$)		
	2 Weeks	3 Months	12 Months	2 Weeks	3 Months	12 Months
Excellent	30.56%(33)	74.07%(80)	76.85%(83)	70.37%(76)	77.78%(84)	79.63%(86)
Good	21.30%(23)	12.04%(13)	12.04%(13)	14.81%(16)	14.81%(16)	15.74%(17)
Fair	31.48%(34)	7.41%(8)	5.56%(6)	9.26%(10)	4.63%(5)	2.78%(3)
Poor	16.67%(18)	6.48%(7)	5.56%(6)	5.56%(6)	2.78%(3)	1.85%(2)
Times in hospital		7 ± 1.39 (days)			16 ± 1.41 (days)	
Mean cost		4106 ± 305.93(¥)			9989 ± 1614.36(¥)	

The number and the percentage of patients of different outcomes after the treatment were showed.

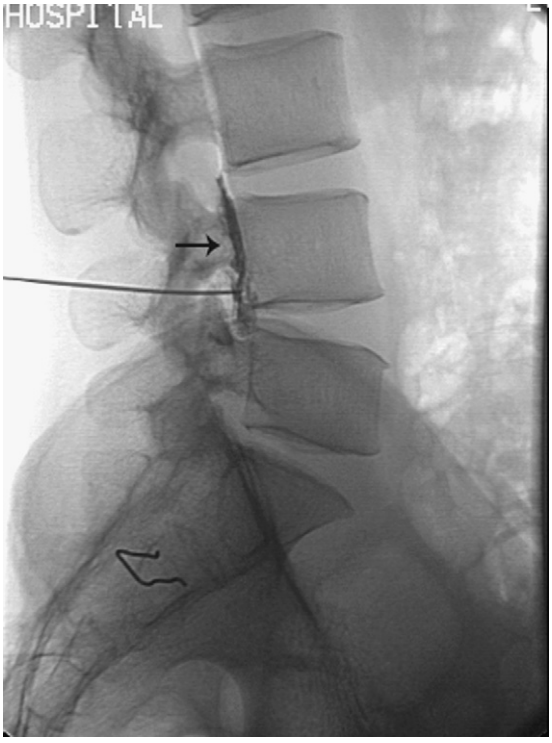

Fig. 3. The lateral position of the needle. The lateral position of the needle after the trans-foramen acupuncture was showed. The arrow showed the contrast spread into the epidural space.

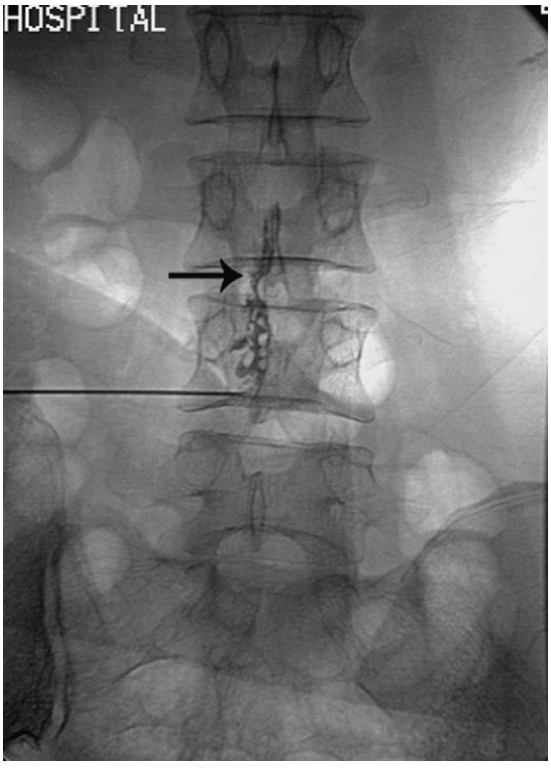

Fig. 4. The anteroposterior position of the needle. The anteroposterior position of the needle after the trans-foramen puncture was showed. The arrow showed the contrast spread into the epidural space.

or good outcome) in 86.11% (93 of 108) and 88.89% (96 of 108) at 3 and 12 months. In group B, treatment was a success in 92.59% (100 of 108) and 95.37% (103 of 108) at 3 and 12 months. By 3 and 12 months, the success rate was a little higher in group B, but there was no statistically significant difference in outcome between two groups ($P = 0.123$, $P = 0.08$). However, group B produced a statistically significant greater improvement for back pain and disability in the first few weeks ($P = 0.0001$). In group A, treatment was a success in 51.86% (56 of 108) at 2 weeks, but in group B, treatment was a success in 85.18% (92 of 108). Crude cost analysis suggested an overall financial advantage from non-surgical group, and the times in hospital of patients were shorter in the non-surgical group too ($P < 0.01$). There were no serious complications occurred in both two groups. There were no nerve root injuries or infections that occurred in both groups. Table 3 showed the results of the two groups after the treatment.

Patients with an excellent outcome at non-surgical group were asked to perform CT scan after the treatment, Figs. 5–8 were the representative of the CT before and after the treatment. The CT clearly showed the shrinking of the protrusion after the chemonucleolysis.

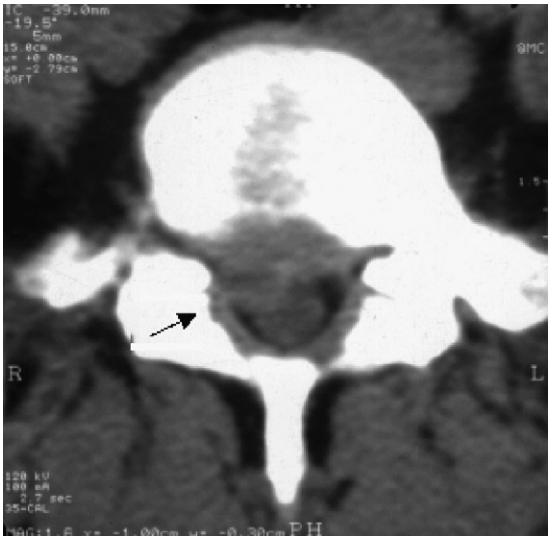

Fig. 5. The CT scan before the treatment. The arrow showed size and position of L4–5 lumbar disc herniation before the treatment.

Please cite this article in press as: Wu Z, et al. Percutaneous treatment of non-contained lumbar disc herniation by injection of oxygen–ozone combined with collagenase. Eur J Radiol (2008), doi:10.1016/j.ejrad.2008.07.029

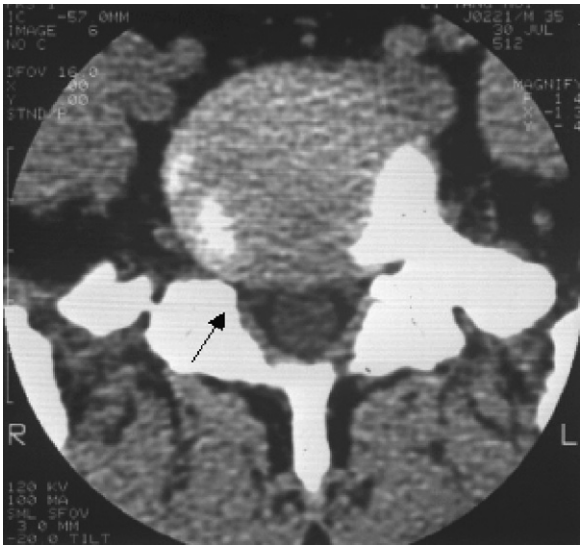

Fig. 6. The CT scan after the treatment. The arrow showed size and position of L4–5 lumbar disc herniation after the treatment at the 12 months.

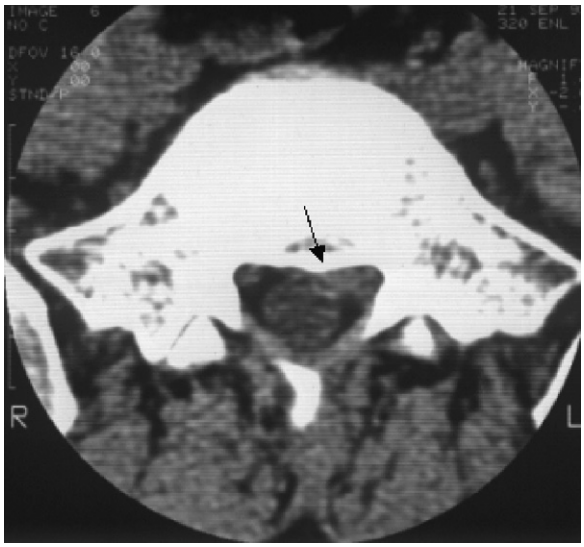

Fig. 8. The CT scan after the treatment. The arrow showed size and position of L5–S1 lumbar disc herniation after the treatment at the 12 months.

4. Discussion

It has been proved that chemonucleolysis can improve the clinical outcomes of lumbar disc herniation [5]. Currently, the materials for the chemonucleolysis include chymopapain [13], collagenase [14], ethanol [6], and ozone [4,15,16] and hypertonic saline [7]. The chymopapain was the first proteinase used for the treatment of lumbar disc herniation, it was mainly used by intradiscal injection to lyse the proteoglycan of lumbar disc. But chymopapain has a little higher allergy reaction with similar effective rate compared to collagenase [14], it was no longer available in the United States [11]. Collagenase can specifically lyse collagen, which is one of the main compositions of the protrusion; therefore, collagenase has been used to treat the lumbar disc herniation [16]. And recently, ozone was reported can also improve the clinical outcomes of lumbar disc herniation. But the success rates of all these procedures are still unsatisfied. The published data showed [17,18] that the success rate of ozone for the treatment of lumbar disc herniation was only around 68% to 76%, and the success rate of collagenase for the treatment of lumbar disc herniation was from 70% to 75% [19,20]. To improve the success rates, we combined ozone with collagenase together to treat lumbar disc herniation, and our results suggested the combination was successful. The success rate in our group was 88.9%, which was significantly higher than the reported success rate. And the success rate in our group was close to the success rate in the surgical group too, although the surgical group produced a statistically significant greater improvement for back pain and disability in the first few weeks ($P < 0.01$), however the success rate in the minimally invasive group at the 3 and 12 months was no statistical difference compared to surgical group ($P > 0.05$). Meanwhile, the minimally invasive procedure has more advantages compared to the surgical procedure: Chemonucleolysis with the combination of ozone and collagenase has little trauma compared to the surgery. The minimally invasive procedures can be completed with a thin needle (22G), so it has very little trauma. Collagenase can specifically lyse collagen to shrink the protrusion and release the mechanical pressure to the nerve. Ozone not only can directly oxidize the proteoglycan, which is another kind of majorities of the macromolecular material in the nucleus, but also can degenerate nucleus cells and finally lyses the cells, so the ozone can also decompress lumbar disc and release the mechanical pressure of the protrusion to the nerves [15,16]. On the hand, the ozone can alleviate the pain by decreasing the inflammation response and improving the inflammation [14], which had been suggested to be involved in the mechanism. Therefore this combination will enhance the role of chemonucleolysis and improve the success rate. In fact, the success rate (88.9%) in our group was significantly higher than the reported success rate. It is very safe with little complications. In our group, no serious complications occurred. No nerve injuries occurred. It has overall financial advantages compared to the surgical group. The times in the hospital of the patients or the mean cost in the minimal invasive group were shorter or lower than its in the surgical group.

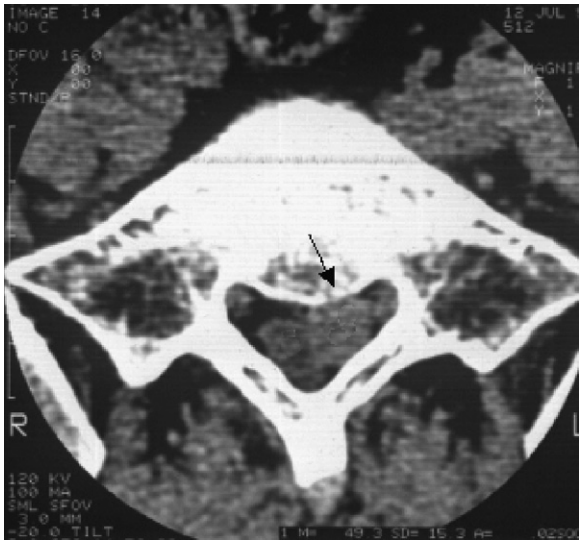

Fig. 7. The CT scan before the treatment. The arrow showed size and position of L5–S1 lumbar disc herniation before the treatment.

Although minimally invasive procedure has more advantages compared to the surgical procedure, but each method has their indications and contraindications, so we must remember that this minimally invasive procedure is not good for all the patients with lumbar disc herniation. For the patients with stenosis of vertebral canal, protrusion calcification and lateral access stenosis, must be treated with surgery. In our group, all patients had a typical clinical

Please cite this article in press as: Wu Z, et al. Percutaneous treatment of non-contained lumbar disc herniation by injection of oxygen–ozone combined with collagenase. Eur J Radiol (2008), doi:10.1016/j.ejrad.2008.07.029

symptoms and signs: one leg pain or two legs pain with a positive strait-raising-test, and CT or MRI showed a clear lumbar disc herniation.

The reason of 12 patients who did not get a good effect in minimally invasive group was analyzed: 2 patients did not keep a body position after the procedure of chemonucleolysis, which would lead to the diffuse of the collengenase to other area and reduce the concentration of collengenase in the protrusion area; 3 patients has a little longer history (5–6 years with the atrophy of muscle of leg); 2 patients was with a very huge protrusion, 1200 u collengenase maybe was not enough to lyse the protrusion; 5 patients were not followed the doctor's advice after the treatment and continued to raise the heavy lift.

In conclusion, the combination of the collagenase with ozone shows statistically significant reductions in pain and improvements in function, and because the success rate in minimally invasive group at 3 and 12 months was no difference compared to the surgery, it can be considered as an option for the treatment of non-contained lumbar disc herniation, at least in the absence of clear indications for surgery.

Acknowledgments

The authors thank Liu yufeng for the help with the equipment. The authors also thank Dr. Ge for the preview of manuscript.

References

[1] Zentner J, Schneider B, Schramm J. Efficacy of conservative treatment of lumbar disc herniation. J Neurosurg Sci 1997;41(3):263–8.
[2] Boccanera L, Laus M. Chemonucleolysis: advantages and disadvantages. Chir Organi 1990;75(1):25–32.
[3] Andreula C, Muto M, Leonardi M. Interventional spinal procedures. Eur J Radiol 2004;50(2):112–9.
[4] Buric J, Molino Lova R. Ozone chemonucleolysis in non-contained lumbar disc herniations: a pilot study with 12 months follow-up. Acta Neurochir Suppl 2005;92:93–7.
[5] Shah NH, Dastgir N, Gilmore MF. Medium to long-term functional outcome of patients after chemonucleolysis. Acta Orthop Belg 2003;69(4):346–9.
[6] Riquelme C, Musacchio M, Mont'Alverne F, et al. Chemonucleolysis of lumbar disc herniation with ethanol. J Neuroradiol 2001;28(4):219–29.
[7] Sato K, Nagata K, Ariyoshi M, et al. Intradiscal pressure after intradiscal injection of hypertonic saline: an experimental study. Eur Spine J 2000;9(3):213–7.
[8] Mochida J, Toh E, Nomura T, et al. The risks and benefits of percutaneous nucleotomy for lumbar disc herniation. A 10-year longitudinal study. J Bone Joint Surg Br 2001;83(4):501–5.
[9] Choy DS. Percutaneous laser disc decompression (PLDD): twelve years' experience with 752 procedures in 518 patients. J Clin Laser Med Surg 1998;16(6):325–31.
[10] Troussier B, Lebas JF, Chirossel JP, et al. Percutaneous intradiscal radiofrequency thermocoagulation. A cadaveric study. Spine 1995;20(15):1713–8.
[11] Reddy Arra S, Loh Shaun, Cutts Jennifer, Rachlin Jacob, Hirsch Joshua A. New approach to the management of acute disc herniation. Pain Physician 2005;8:385–9.
[12] Le Hoang, Faheem A, Sandhu F. Clinical outcomes after minimal-access surgery for recurrent lumbar disc herniation. Neurosurg Focus 2003;15(3):1–4.
[13] Aribit F, Charissoux JL, Arnaud JP. Long-term 10-year outcome after chemonucleolysis for lumbar disc herniation. Rev Chir Orthop Reparatrice Appar Mot 2002;88(3):221–8.
[14] Hedtmann A, Steffen R, Kramer J. Prospective comparative study of intradiscal high-dose and low-dose collagenase versus chymopapain. Spine 1987;12(4):388–92.
[15] Muto M, Andreula C, Leonardi M. Treatment of herniated lumbar disc by intradiscal and intraforaminal oxygen–ozone (O2–O3) injection. J Neuroradiol 2004;31(3):183–9.
[16] Paradiso R, Alexandre A. The different outcomes of patients with disc herniation treated either by microdiscectomy, or by intradiscal ozone injection. Acta Neurochir Suppl 2005;92:139–42.
[17] D' Erne M, Scarchilli A, Artale AM, et al. Ozone therapy in lumbar sciatic pain. Radiol Med Torino 1998;95(1–2):21–4.
[18] Muto M, Avella F. Percutaneous treatment of herniated lumbar disc by intradiscal oxygen–ozone injection. Interventional Neurorradiol 1998;4(2):273–86.
[19] Chu KH. Collagenase chemonucleolysis via epidural injection. A review of 252 cases. Clin Orthop Relat Res 1987;215:99–104.
[20] Hedtmann A, Fett H, Steffen R, et al. Chemonucleolysis using chymopapain and collagenase. 3-year results of a prospective randomized study. Z Orthop Ihre Grenzgeb 1992;130(1):36–44.

Please cite this article in press as: Wu Z, et al. Percutaneous treatment of non-contained lumbar disc herniation by injection of oxygen–ozone combined with collagenase. Eur J Radiol (2008), doi:10.1016/j.ejrad.2008.07.029