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Efficacy of an ethyl alcohol gel in symptomatic disc herniation

Stefano Marcia[a], Matteo Bellini[b], Joshua A. Hirsch[c], Ronil V. Chandra[d], Emanuele Piras[a], Mariangela Marras[e], Anna Maria Sanna[f], Luca Saba[g,*]

[a] Radiology Dept. SS Trinità Hospital, ATS Sardegna, ASSL Cagliari, Italy
[b] Neuroimaging and Neuro-Interventional Unit, Hospital Santa Maria alle Scotte, Siena, Italy
[c] Neuroendovascular Program, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States
[d] Neurovascular Surgery and Neuroradiology Services (R.V.C.), Monash Health, Monash University, Melbourne, Australia
[e] Radiology Unit Microcitemico Hospital, AOB Cagliari, Italy
[f] Physical Therapy Unit, SS Trinità Hospital, ATS Sardegna, ASSL Cagliari, Italy
[g] Department of Radiology, University of Cagliari, Italy

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ABSTRACT

Purpose: To evaluate the clinical outcome of DiscoGel® chemonucleolysis for symptomatic disc herniation in patients who fail conservative treatment.

Material and methods: Consecutive patients with symptomatic disc herniation confirmed on MRI who failed conservative management for at least 6 months were included. Visual analogue scale (VAS), Oswestry Disability Index (ODI) scores, and analgesic use were recorded at baseline, and 12 months after treatment. Multidetector CT (MDCT) was performed at baseline, and 12 months after treatment to assess for DiscoGel® extravasation and alteration in treated disc volume. In a unique long-term subgroup analysis of 31 patients, telephonic follow-up was performed utilizing VAS and ODI parameters 7 years after the procedure.

Results: A total of 87 disc herniations were treated in 71 patients; majority (54%) were treated at L4/5 and L5/S1. VAS score of 8 before treatment was reduced to 3 at 12 months after treatment ($p = 0.0001$); ODI score of 51 before treatment was reduced to 15 at 12 months after treatment ($p = 0.0001$). Analgesic use of 70.4% was reduced to 29.6% after treatment. There were no symptomatic procedural complications; MDCT revealed 1 asymptomatic peri-neural DiscoGel® extravasation. In the 31 subjects that underwent telephonic follow-up the VAS and ODI parameters maintained their values without statistically significant differences when compared with the 12-month follow-up.

Conclusion: Patients with symptomatic disc herniation who failed conservative treatment and were treated with DiscoGel® chemonucleolysis achieved significant gains in pain relief and reduced disability without symptomatic complication. DiscoGel® chemonucleolysis is a feasible, minimally invasive technique for treatment of symptomatic disc herniation.

1. Introduction

Back pain (BP) is one of the most common disorders worldwide with significant impact on public health [1,2]. It is estimated that about 80% of adults in western world will suffer BP at some points in their lives [3]. One of the most frequent causes of BP is disc herniation (DH), which triggers pain pathways via mechanical compression together with immunologic and inflammatory changes [4,5].

Over the years, several therapies have emerged to treat DH, ranging from conservative treatment to minimally invasive and percutaneous techniques to open surgical methods [6–8]. Although conservative treatment is the mainstay of management for most patients, there is growing concern regarding the use of opioid therapy in this and other populations [30,31]. Beyond that, persistent pain (more than 6 months) often leads to consideration of minimally invasive techniques and/or open surgery. Although open surgery can be effective (49–95%), it also carries the risks of general anaesthesia, high cost and significant post-operative complications, including new or worsening of neurological deficit of 1–3%, and re-operation rates of 4–10% [9–11,35].

As an alternate to surgical therapy, a number of minimally invasive procedures have been considered with dramatic increases in utilization over the years. These include chemonucleosis [12]; percutaneous laser disc decompression (PLDD) [13]; automated percutaneous lumbar discectomy (APLD) [14,32]; intradiscal electrothermal therapy (IDET)

* Corresponding author: Department of Radiology, Azienda Ospedaliero Universitaria of Cagliari, SS 554 Monserrato, Cagliari, Italy.
E-mail address: lucasaba@tiscali.it (L. Saba).

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[15]; percutaneous coblation nucleoplasty [16,33] and others [17,18,34]. Most of these procedures aim to reduce the volume and/or pressure of the disc tissue, relieving the disc herniation without affecting spinal canal.

An emerging minimally invasive procedure is the use of DiscoGel®, a radiopaque gelified ethanol, for symptomatic DH [19,20]. Previously published papers have demonstrated the necrotizing effect on biological tissues of the ethanol that has long been used in interventional procedures [21–23]. In the nucleus pulposus, ethanol produces a molecular scission of proteoglycans and glycosaminoglycans that leads to a degradation of these components and a loss of their water-retaining capacity resulting in dehydration and chemical decompression of the disc [24]. Nevertheless, ethanol does carry two major drawbacks: 1) the excessive diffusivity and 2) the lack of radiopacity leading to blind injection [20]. Together, these issues severely limit use of ethanol. DiscoGel® was developed to overcome the 2 drawbacks associated with ethanol injection, and includes ethylcellulose to make the alcohol solution more viscous and tungsten to facilitate radiological monitoring of the injection.

The purpose of the study was to evaluate the clinical outcome of DiscoGel® chemonucleolysis for symptomatic disc herniation in patients who failed conservative treatment.

2. Materials and methods

2.1. Study design and patient population

In this retrospective study, 71 consecutive patients (males 33, females 38; median age 56 ± 11 years, age range 34–82 years) that underwent DiscoGel® chemonucleolysis between October 2009 and January 2011 were included. In accordance with the applicable National Research Ethics Service guidance, ethical approval for the study was not required [25] because the study was performed retrospectively on routinely acquired images and specimens. However, this study was approved by the review board of our Institution.

2.2. Inclusion and exclusion criteria

The inclusion criteria were based on two different parameters: clinical and neuroimaging. Therefore, to perform DiscoGel® we required: (1) presence of back pain, cruralgia and sciatica lasting six months at least and resistant to conservative approach (physical and medical therapies); (2) MRI findings of one or more disc herniations in a location congruent with symptoms, complicated or not by degenerative disc disease.

The exclusion criteria were the MRI findings of calcified herniation or free disc fragments and, the presence of neurological deficit with impaired lower limb mobility congruent with observed disc disease, bleeding disorder, local infection, uncontrolled or degenerative spine disease (spondylolysis and spondylolisthesis), pregnancy and patient refusal [26].

2.3. Technique of procedure

All the procedures were performed in day-surgery with local anaesthesia (2 ml of subcutaneous lidocaine 2%, Pfizer, Latina, Italy). Antibiotics (2 g Cefamizin, Pfizer, Latina, Italy) were administered 30 min before the procedure. The treatment was performed in different phases (Fig. 1): the first one is the disc puncture, performed with an 18 Gauge spinal needle under fluoroscopic guidance using a digital angiography system.

The patients were positioned in the prone position and an extraspinal paravertebral approach was performed for lumbar discs, while for cervical discs an anterolateral approach was used. Oblique views under fluoroscopic guidance allowed good visualization of the target point avoiding injury to the nerve root and to optimize obtaining the correct angle to reach the middle of the nucleous pulposus of the lumbar disc. In cervical disc cases, digital displacement was often utilized to help avoid the carotid artery, jugular vein, trachea and the esophagus. Prior to injection, the correct position of the needle was confirmed with AP and Lateral radiographs. Then, 0.8 ml of Discogel for lumbar discs and 0.3 ml for cervical were injected into the nucleus pulposus under continuous fluoroscopic guidance: its radio-opacity facilitates confirmation of the spread of the material within the disc and helps to avoid epidural leakages.

2.4. DiscoGel®

Is a sterile viscous solution containing ethyl alcohol, cellulose derivative product and tungsten, a radio-opaque element. The 96% pure ethyl alcohol produces a local necrosis of the nucleus pulposus. Its action is mechanical via a dehydration of the turgescent and protruding disc. The DiscoGel® has a double mechanism of action on the intervertebral disc: a hydrophilic power conferring a fluidal migration from the periphery of the disc, notably from hernia toward the nucleus pulposus, which corresponds to the site of injection of the gel, and a simultaneous deposition of part of the gel which precipitates and makes a prosthesis at the injection site. Each vial of DiscoGel contains 2 mL of material. 0.8/0.3 mL are predictably used for Lumbar and Cervical injections respectively.

2.5. Data collection

Demographic data, including age, weight, and BMI were obtained. Vital signs at the time of admission and during the procedure were collected. Pain score (using visual analogue scale, VAS), functional ability score (using Oswestry Disability Index, ODI were recorded before the procedure and after 12 months. The use of analgesic drugs (non-opioids) for each patient before and after the treatment was recorded. VAS and ODI analysis were also performed in follow-up at 7-years post-procedure.

2.6. CT measurement

CT was performed before and after the procedure and the height of the disc acquired in 3 different portions of the disc (anterior, medial, posterior) were reviewed by a radiologist who was blinded to the technique with 5 years of experience (Fig. 2). In order to assess the reproducibility, the measurements were acquired two times for both datasets after one week. Moreover, disc volume was calculated using dedicated software (Osirix 7.0, PixMeo).

2.7. Statistical analysis

In this study the normality of each continuous variable group was tested using the Kolmogorov-Smirnov Z test and appropriate tests for Gaussian or non-Gaussian values were selected. For Gaussian values, continuous data were described as the mean value ± SD whereas for non-gaussian values median values and IQR were given. Wilcoxon test was applied to test the difference of VAS and ODI before and after DiscoGel® chemonucleolysis. Wilcoxon was also used to test the difference in height and volume of the discs before and after the procedure. McNemar test was used to test the difference in the use of analgesic drug before and after the treatment. Pearson rho correlation was also test to check the correlation between age / gender and VAS / ODI. Bland Altman plots were calculated to assess the reproducibility of the measurement. Because the normality of the data was confirmed for the disc measurement a student t-test was applied to calculate the difference between disc's height and Bland-Altman Plot was applied to test the reproducibility.

A p value < 0.05 was regarded to indicate statistical significance association and all values were calculated using a two-tailed

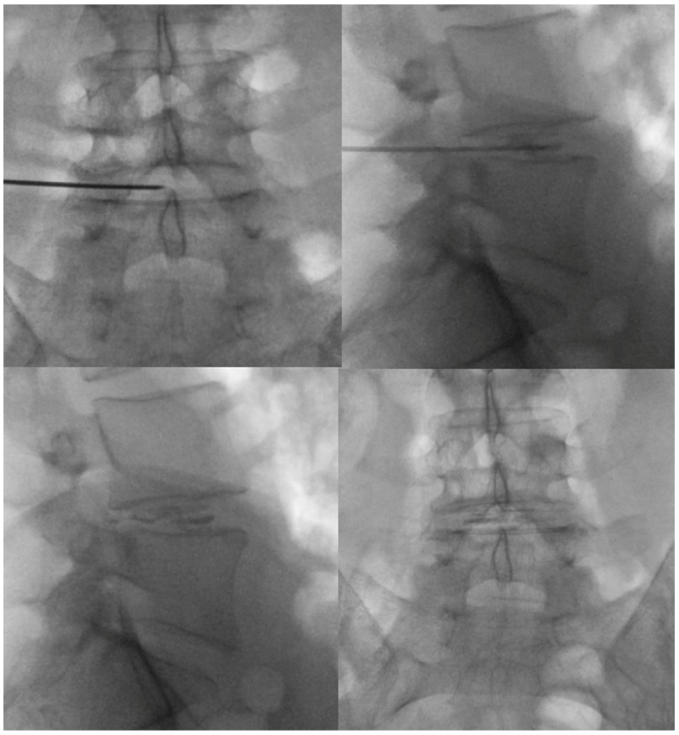

Fig. 1. Injection of the ethanol gel under fluoroscopic guidance.

significance level. *R* software (www.r-project.org) was employed for statistical analyses.

3. Results

3.1. General results

Seventy-one consecutive patients (males 33, females 38) with a median age of 56 ± 11 years (range 34–82 years) entered in the study. In these 71 subjects the number of treated level was 87 because 16 patients underwent to 2 levels treated at the same time. The L5/S1 was treated 38 times, the L4/L5 for 36 times, the L3/L4 for 8 times, the L2/L3 for 2 times, the C6/C7 four times, the C4/C5 for 2 times and the C5/C6 for 1 time. The antero-lateral approach was used in 4 cases (2 C6/C7, one C4/C5 and one C5/C6, all from the right side), in the other cases the paravertebral approach was used (39 from the right and 45 from the left side).

3.2. Clinical results

The median of VAS pain score before intervention was 8 whereas the value after the procedure was 3 (p value = 0.0001). The ODI before the intervention was 51 and after the procedure was 15 (p value = 0.0001). In both cases the box-plot are given in the (Fig. 3). We did not find any correlation between patients' age and VAS or ODI (p = 0.325) and there was no significant difference between males and females in terms of pain score or ODI (p = 0.753 and P = 0.446, respectively). We tested the use of analgesic drug and we found that 54 patients used the analgesic drugs before the procedure (70.4%) and that the number of patients that used the analgesic drugs dropped out to 21 (29.6%) after

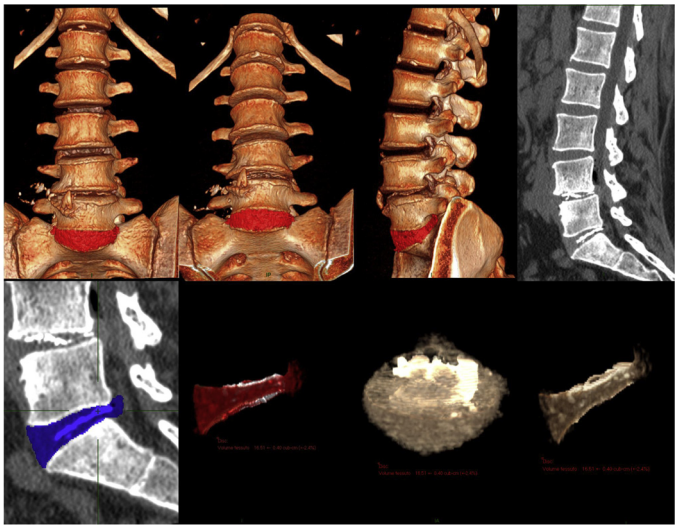

Fig. 2. Disc measurement.

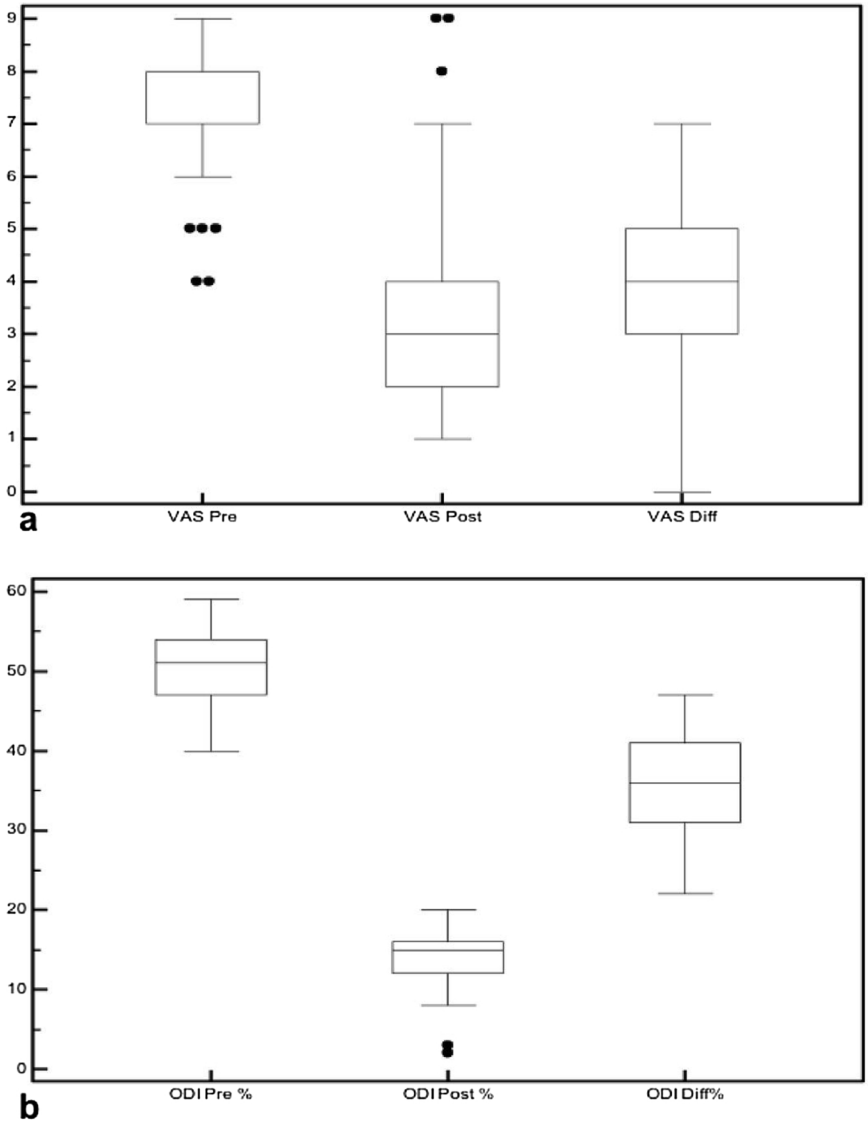

Fig. 3. The box-plot for VAS (panel a) and ODI (panel b) before, after treatment and the difference are given.

the procedure. Particularly noteworthy is that fact that of the 54 patients that used drugs before, 41 completely stopped after placement of Disco-Gel. There were 17 patients that did not use drugs before the procedure. Of the 17, there were 8 patients that required transient use of oral anti-inflammatory agents after the procedure. Uniquely, 31 patients were available to participate in 7 year follow-up. There was no statistically significant differences in VAS (p value = 0.1122) and ODI (p = 0.0996) were found when compared to the 12 month data points. At seven years, the re-intervention rate in the was 12.9% (4 cases of 31).

3.3. Adverse events

There was one case of DiscoGel® extravasation in a 44-year-old male patient that was treated at the L5-S1 level. The Discogel® extravasated close to the exiting left L5 root. This leak was asymptomatic at all time points.

3.4. CT analysis of the disc

The results are summarized in the Table 1. No statistically significant difference was found in disc's height for the anterior, medium and posterior position (Fig. 4). The Bland-Altman plot showed very good reproducibility (Fig. 5). However, in the volume analysis of the disc a statistically significant difference was found (mean volume pre = 10.65; mean volume post = 12.5; p value = 0.0001) (Fig. 6).

Table 1
Student test for disk analysis.

Position	mean pre	mean post	p value
Anterior	7.7	7.6	0.7871
Middle	5.6	5.2	0.0647
Posterior	3.7	3.4	0.2709

4. Discussion

Several factors play a role within the disc space when a DH occurs; both mechanical (the compression of the nerve roots) and biochemical (inflammatory factors or immunological factors). The rationale of the disc shrinkage relays in the reduction of the mechanical compression determined to the nerve roots. In the past, it has been suggested that intra-discal injection of alcohol could be a minimally invasive capable to determine induces disc shrinkage and alleviates nerve root inflammation with short-term and long-term pain relief. The purpose of

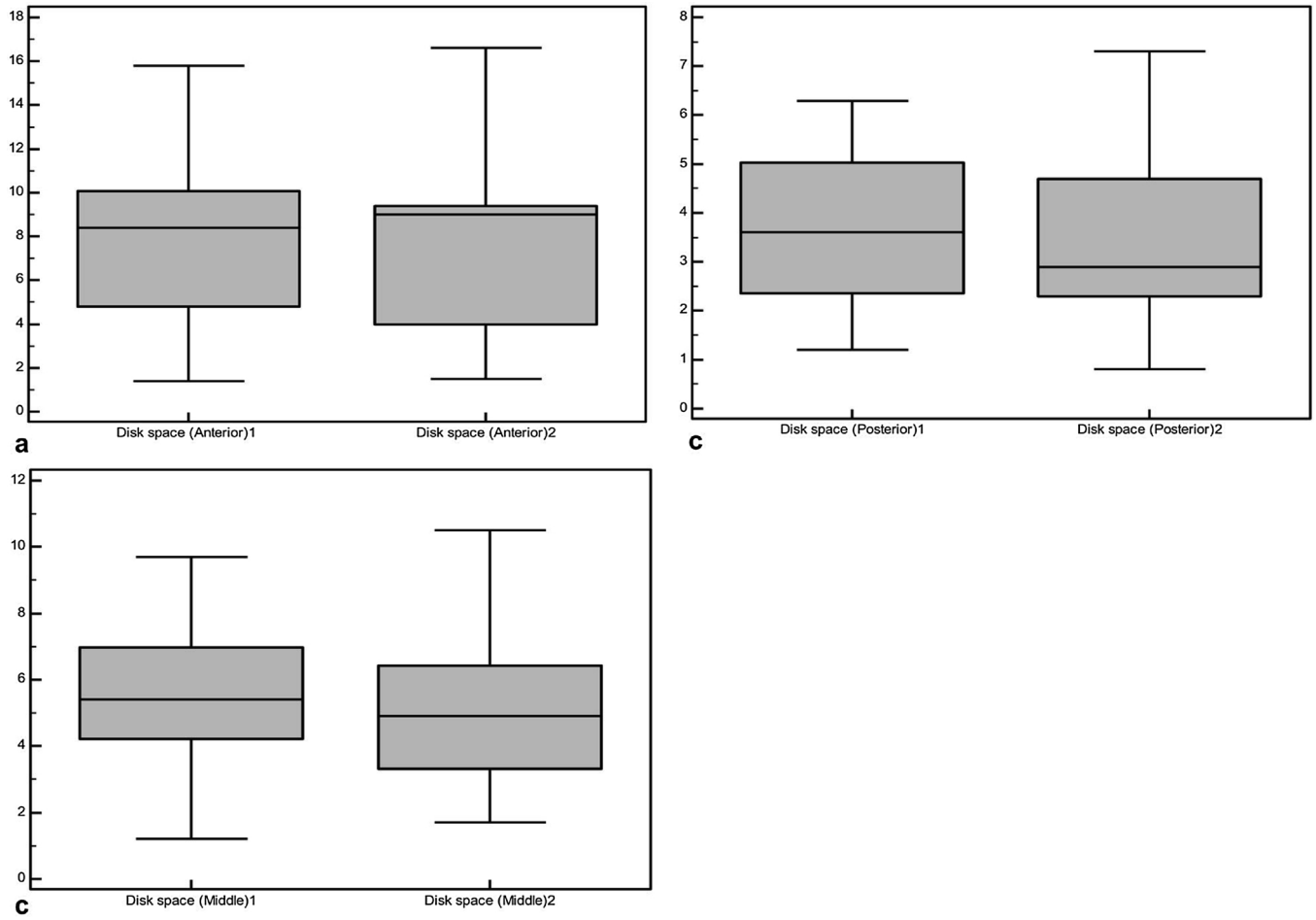

Fig. 4. Boxplot disks.

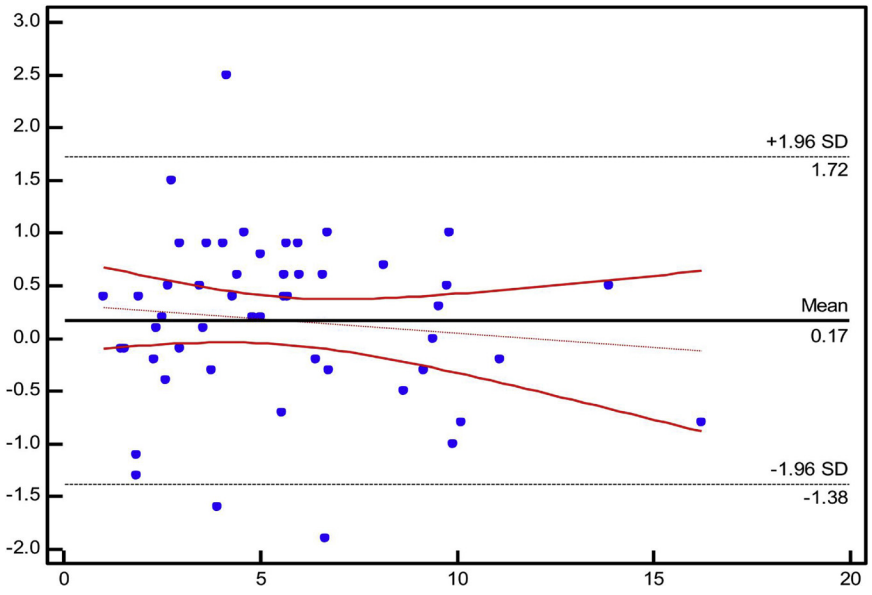

Fig. 5. Bland Altman.

the current study was to assess the therapeutic outcome of DiscoGel® chemonucleolysis in patients with DH un-responsive to conservative therapy.

The patient cohort is similar to the population by Singh et al. [29] and most of the treated levels in this study were L5\S1 (43.7%) and L4\L5 (41.4%) whereas the cervical levels were treated in only 5 patients. Multiple-level treatments were performed in circumstances where clinical symptoms and signs corresponded to levels that could be treated on advanced imaging, i.e., MRI. This occurred in both the cervical and lumbar spine. The single 2 mL vial of DiscoGel is sufficient

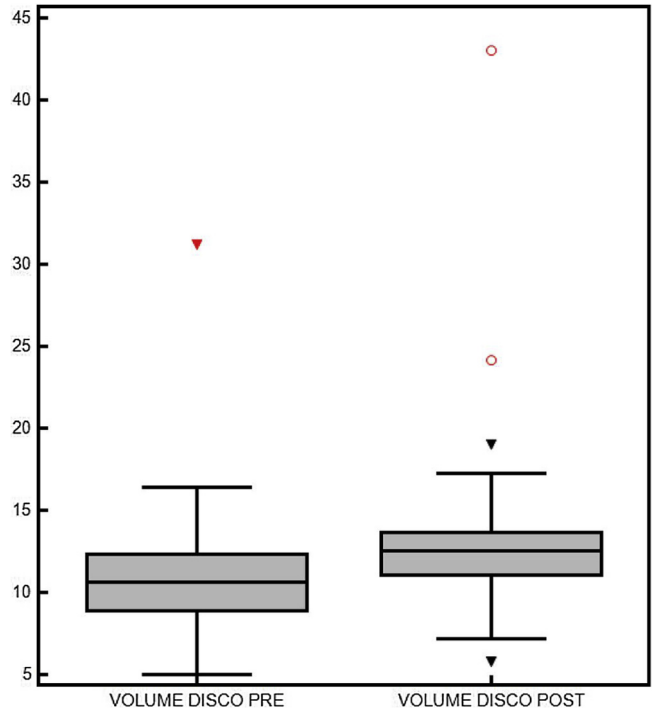

Fig. 6. Boxplot disk volume.

material for all cases in this series that required injection of more than level.

It is important to underline that the technical approach to treat the disc in the cervical level is different from the lumbar ones. When DiscoGel® chemonucleolysis was performed in cervical level an antero-lateral approach was performed in the 80% of cases whereas for the lumbar level the paravertebral approach was always used.

We found that the treatment produces excellent results in both the pain (the median of VAS pain score before intervention was 8 whereas the value after the procedure was 3 (p value = 0.0001)) and also in the functional ability score (ODI before the intervention was 51 and after the procedure was 15 (p value = 0.0001)). These results are concordant with previous paper published by Hashemi et al. [1]. In a study by Gallucci et al. [27] the treatment with intradiscal and intraforaminal injection of steroid and oxygen-ozone versus steroid alone were compared and they found excellent results by suggesting that the disc could represent an excellent target to determine pain relief in patients with DH. By comparing the VAS of our study we found that our patients had the pre-procedural VAS higher compared to the population of other studies. In the study by Singh et al. [29] the pre-procedural VAS value was 6.8. Our findings are similar with recently published studies [36–38].

We tested the use of analgesic drug and we found that 54 patients used the analgesic drugs before the procedure (70.4%) and that the number of patients that used the analgesic drugs dropped out to 21 (29.6%) after the procedure. In particular, of the 54 patients that used drugs before, 41 stopped. Of the 17 patients that did not use drug before the procedure 8 started to use it.

In our analysis we did not find a statistically significant difference in discal height for the anterior, medium and posterior position whereas a statistically significant difference was found when the volume was considered. This is important because it clearly demonstrated that in this type of analysis the measurement of the height, even if taken at different level, is not representative of the entire effect of the procedure to the disc whereas the volume analysis correctly depict it.

When invasive or minimally-invasive approaches are tested it is fundamental also to verify the presence of complications. In our cohort in only one case we observed a complication after the procedure: the extravasation of DiscoGel® involving the tissue close to the left root. The patient did not show sign of clinical damage. When other minimally invasive procedures are performed to the disc, complications reported include discitis, anaphylaxis, instability, increased back pain, epidural fibrosis, and reherniation [28]. The complication rate described using coblation nucleoplasty for herniated cervical discs is 0.8% and for herniated lumbar discs 1.8%. In the case of this series, we are injecting a substance and believe the complication profile of a single, verifiable leak which resulted in no untoward symptoms or signs compares reasonably and favourably with other reported techniques. Additional complications that have been described in the literature for percutaneous disc decompression include, infection and hematoma as well as direct needle trauma to a spinal nerve with or without persistent paraesthesia. We believe that use of a small bore 18-Gauge needle, strict aseptic conditions and vigilant attention to radiographic anatomy mitigates many of these risks [28].

Of note, eight patients reported increased pain for two or three weeks after the procedure requiring the use of oral analgesic drugs for that finite period of time. This has not been reported in historical series of percutaneous disc decompression. We speculate that the gel injected (even if the small volume used in the procedures) might lead to an increased pressure inside the intervertebral disc and/or inflammatory reaction. We further hypothesize that since the gel undergoes 10–15% volume reduction after 2–3 weeks, the requirement for oral analgesics is transient.

There are limitations to our study. First, this is a retrospective study; the patient inclusion was performed according to the Hospital's guidelines but a prospective randomized study would enhance our understanding of the benefits and risks of the procedure. Second, while this is to our knowledge the largest population of disc patients (n = 71) treated with discogel, further analysis with a larger population is necessary to confirm these results. Third, including patients with both cervical and lumbar disc herniations introduces heterogeneity into the study population; cervical and lumbar disc herniations do not behave identically and Disc-osteophyte complexes are more commonly the cause of nerve root compression in the cervical spine compared to the lumbar spine. Finally, ours is an experienced center perhaps indicating that there may be limitations in the generalizability of these results; particularly in term of the prevalence of procedure related complications.

5. Conclusion

Our study suggests that DiscoGel® injection is a feasible technique for the treatment of disc herniation. While pain and disability were meaningfully improved, no clinical complications were observed. A prospective, randomized control trial is warranted.

Conflict of interest statement

None.

Ethical approval statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent statement

Informed consent was obtained from all individual participants included in the study.

References

[1] M. Hashemi, M. Poorfarokh, S.A. Mohajerani, P. Jalili, V. Akhyani, A. Barikani, F. Farivar, Injection of intradiscal o2-o3 to reduce pain and disability of patients with low back pain due to prolapsed lumbar disk, Anesth. Pain Med. 4 (November (5)) (2014) e19206, , https://doi.org/10.5812/aapm.19206.

[2] N. Fouquet, A. Descatha, C. Ha, A. Petit, Y. Roquelaure, An epidemiological surveillance network of lumbar disc surgery to help prevention of and compensation for low back pain, Eur. J. Public Health (January) (2016) pii: ckv240. [Epub ahead of print] PubMed PMID: 26733628.

[3] N. Gouveia, A. Rodrigues, M. Eusébio, S. Ramiro, P. Machado, H. Canhão, J.C. Branco, Prevalence and social burden of active chronic low back pain in the adult Portuguese population: results from a national survey, Rheumatol. Int. (December) (2015) [Epub ahead of print] PubMed PMID: 26661091.

[4] R. Freynhagen, R. Baron, The evaluation of neuropathic components in low back pain, Curr. Pain Headache Rep. 13 (June (3)) (2009) 185–190.

[5] J.H. Zheng, E.T. Walters, X.J. Song, Dissociation of dorsal root ganglion neurons induces hyperexcitability that is maintained by increased responsiveness to cAMP and cGMP, J. Neurophysiol. 97 (January (1)) (2007) 15–25.

[6] D. Vanni, F.S. Sirabella, M. Guelfi, A. Pantalone, R. Galzio, V. Salini, V. Magliani, Microdiskectomy and translaminar approach: minimal invasiveness and flavum ligament preservation, Global Spine J. 5 (April (2)) (2015) 84–92.

[7] L. Cong, Y. Zhu, G. Tu, A meta-analysis of endoscopic discectomy versus open discectomy for symptomatic lumbar disk herniation, Eur. Spine J. (January) (2015) [Epub ahead of print] PubMed PMID: 25632840.

[8] D. Erginousakis, D.K. Filippiadis, A. Malagari, A. Kostakos, E. Brountzos, N.L. Kelekis, A. Kelekis, Comparative prospective randomized study comparing conservative treatment and percutaneous disk decompression for treatment of intervertebral disk herniation, Radiology 260 (August (2)) (2011) 487–493.

[9] Y. Aydin, I.M. Ziyal, H. Duman, C.S. Turkmen, M. Basak, Y. Sahin, Clinical and radiological results of lumbar microdiskectomy technique with preserving of ligamentum flavum comparing to the standard microdiskectomy technique, Surg. Neurol. 57 (2002) 5–13 discussion 13-14.

[10] S.M. Bhagia, C.W. Slipman, M. Nirschl, Z. Isaac, O. El-Abd, L.S. Sharps, C. Garvin, Side effects and complications after percutaneous disc decompression using coblation technology, Am. J. Phys. Med. 85 (2006) 6–13.

[11] R. Dullerud, P.H. Nakstad, Side effects and complications of automated percutaneous lumbar nucleotomy, Neuroradiology 39 (1997) 282–285.

[12] P. Bełdziński, J. Dzierzanowski, P. Słoniewski, Lumbar disc surgery in historical perspective, Ortop. Traumatol. Rehabil. 6 (June (3)) (2004) 382–384.

[13] D.S. Choy, Percutaneous laser disc decompression (PLDD): 352 cases with an 8 1/2-year follow-up, J. Clin. Laser Med. Surg. 13 (February (1)) (1995) 17–21.

[14] C.W. Park, J.Y. Lee, W.J. Choi, S.K. Chang, Percutaneous disc coagulation therapy (PDCT) comparing with automated percutaneous lumbar discectomy (APLD) in patients of herniated lumbar disc disease: preliminary report, Korean J. Spine 9 (September (3)) (2012) 159–164.

[15] S. Fukui, K. Nitta, N. Iwashita, H. Tomie, S. Nosaka, O. Rohof, Results of intradiscal pulsed radiofrequency for lumbar discogenic pain: comparison with intradiscal electrothermal therapy, Korean J. Pain 25 (July (3)) (2012) 155–160.

[16] B.J. Freeman, R. Mehdian, Intradiscal electrothermal therapy, percutaneous discectomy, and nucleoplasty: what is the current evidence? Curr. Pain Headache Rep. 12 (January (1)) (2008) 14–21.

[17] M.V. Boswell, A.M. Trescot, S. Datta, D.M. Schultz, H.C. Hansen, S. Abdi, N. Sehgal, R.V. Shah, V. Singh, R.M. Benyamin, V.B. Patel, R.M. Buenaventura, J.D. Colson, H.J. Cordner, R.S. Epter, J.F. Jasper, E.E. Dunbar, S.L. Atluri, R.C. Bowman, T.R. Deer, J.R. Swicegood, P.S. Staats, H.S. Smith, A.W. Burton, D.S. Kloth, J. Giordano, L. Manchikanti, American Society of Interventional Pain Physicians, Interventional techniques: evidence-based practice guidelines in the management of chronic spinal pain, Pain Physician 10 (January (1)) (2007) 7–111.

[18] S.H. Sanders, R.N. Harden, P.J. Vicente, Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients, Pain Pract. 5 (December (4)) (2005) 303–315.

[19] J. Théron, H. Cuellar, T. Sola, et al., Percutaneous treatment of cervical disk hernias using gelified ethanol, Am. J. Neuroradiol. 31 (2010) 1454–1456.

[20] J. Théron, L. Guimaraens, A. Casasco, et al., Percutaneous treatment of lumbar intervertebral disk hernias with radiopaque gelified ethanol: a preliminary study, J. Spin. Disord. Tech. 20 (2007) 526–532.

[21] T. Livraghi, S. Nahum Goldberg, et al., Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection, Radiology 210 (1999) 655–661 [PubMed].

[22] C. Riquelme, M. Musacchio, F. Mont'Alverne, et al., Chemonucleolysis of lumbar disc herniation with ethanol, J. Neuroradiol. 28 (2001) 219–229 [PubMed].

[23] J.C. Wojak, J.J. Connors III, Nerve blocks and discectomy, in: J.J. Connors, IIIJ.C. Wojak (Eds.), Interventional Neuroradiology: Strategies and Practical Technique, WB Saunders, London, 1999, pp. 421–423.

[24] M. Muto, G. Guarnieri, G. De Dominicis, Intradiscal and intramuscular injection of DiscoGel® - radiopaque gelified ethanol: pathological evaluation, Neuroradiol. J. 23 (2010) 249–252.

[25] National Research Ethics Service, Approval for Medical Devices Research: Guidance for Researchers, Manufacturers, Research Ethics, Committees and NHRR&D Offices. (Version 2), National Patients Safety Agency, London, England, 2008.

[26] S. Stagni, F. de Santis, L. Cirillo, M. Dall'olio, C. Princiotta, L. Simonetti, A. Stafa, M. Leonardi, A minimally invasive treatment for lumbar disc herniation: DiscoGel® chemonucleolysis in patients unresponsive to chemonucleolysis with oxygen-ozone, Interv. Neuroradiol. 18 (March (1)) (2012) 97–104.

[27] M. Gallucci, N. Limbucci, L. Zugaro, A. Barile, E. Stavroulis, A. Ricci, et al., Sciatica: treatment with intradiscal and intraforaminal injections of steroid and oxygen-ozone versus steroid only, Radiology 242 (3) (2007) 907–1.

[28] M. Smuck, B. Benny, A. Han, J. Levin, Epidural fibrosis following percutaneous disc decompression with coblation technology, Pain Physician 10 (September (5)) (2007) 691–696.

[29] V. Singh, C. Piryani, K. Liao, S. Nieschulz, Percutaneous disc decompression using coblation (nucleoplasty) in the treatment of chronic discogenic pain, Pain Physician 5 (July (3)) (2002) 250–259.

[30] L. Manchikanti, A.M. Kaye, N.N. Knezevic, H. McAnally, K. Slavin, A.M. Trescot, S. Blank, V. Pampati, S. Abdi, J.S. Grider, A.D. Kaye, K.N. Manchikanti, H. Cordner, C.G. Gharibo, M.E. Harned, S.L. Albers, S. Atluri, S.M. Aydin, S. Bakshi, R.L. Barkin, R.M. Benyamin, M.V. Boswell, R.M. Buenaventura, A.K. Calodney, D.L. Cedeno, S. Datta, T.R. Deer, B. Fellows, V. Galan, V. Grami, H. Hansen, S. Helm Ii, R. Justiz, D. Koyyalagunta, Y. Malla, A. Navani, K.H. Nouri, R. Pasupuleti, N. Sehgal, S.M. Silverman, T.T. Simopoulos, V. Singh, D.R. Solanki, P.S. Staats, R. Vallejo, B.W. Wargo, A. Watanabe, J.A. Hirsch, Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines, Pain Physician 20 (February (2S)) (2017) S3–S92.

[31] L. Manchikanti, V. Pampati, J.A. Hirsch, Utilization of interventional techniques in managing chronic pain in medicare population from 2000 to 2014: an analysis of patterns of utilization, Pain Physician 19 (May (4)) (2016) E531–46 PMID: 27228520.

[32] J.A. Hirsch, V. Singh, F.J. Falco, R.M. Benyamin, L. Manchikanti, Automated percutaneous lumbar discectomy for the contained herniated lumbar disc: a systematic assessment of evidence, Pain Physician 12 (May-Jun (3)) (2009) 601–620 Review. PMID: 19461826.

[33] L. Manchikanti, F.J. Falco, R.M. Benyamin, D.L. Caraway, T.R. Deer, V. Singh, H. Hameed, J.A. Hirsch, An update of the systematic assessment of mechanical lumbar disc decompression with nucleoplasty, Pain Physician 16 (April (2 Suppl)) (2013) SE25–54 Review.

[34] L. Manchikanti, V. Singh, A.K. Calodney, S. Helm 2nd, T.R. Deer, R.M. Benyamin, F.J. Falco, J.A. Hirsch, Percutaneous lumbar mechanical disc decompression utilizing Dekompressor®: an update of current evidence, Pain Physician 16 (April (2 Suppl)) (2013) SE1–24 Review. PMID: 23615884.

[35] M.F. Shriver, J.J. Xie, E.Y. Tye, B.P. Rosenbaum, V.R. Kshettry, E.C. Benzel, T.E. Mroz, Lumbar microdiscectomy complication rates: a systematic review and meta-analysis, Neurosurg. Focus 39 (October (4)) (2015) E6.

[36] M. Bellini, D.G. Romano, S. Leonini, I. Grazzini, C. Tabano, M. Ferrara, P. Piu, L. Monti, A. Cerase, Percutaneous injection of radiopaque gelified ethanol for the treatment of lumbar and cervical intervertebral disk herniations: experience and clinical outcome in 80 patients, AJNR Am. J. Neuroradiol. 36 (March (3)) (2015) 600–605.

[37] S. Touraine, J. Damiano, O. Tran, J.D. Laredo, Cohort study of lumbar percutaneous chemonucleolysis using ethanol gel in sciatica refractory to conservative treatment, Eur. Radiol. 25 (November (11)) (2015) 3390–3397.

[38] A. Léglise, J. Lombard, A. Moufid, DiscoGel® in patients with discal lumbosciatica. Retrospective results in 25 consecutive patients, Orthop. Traumatol. Surg. Res. 101 (September (5)) (2015) 623–626.