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Meta-Analysis

Nucleoplasty, a Minimally Invasive Procedure for Disc Decompression: A Systematic Review and Meta-analysis of Published Clinical Studies

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Background: Nucleoplasty, based on Coblation® technology, is a minimally invasive procedure used to decompress herniated discs. Reviews to date – exclusively systematic reviews – recommend nucleoplasty for treating chronic back pain, although with the restriction of limited to fair evidence. We therefore aimed to summarize and interpret our calculated results, where possible comprehensively and quantitatively, using statistical methods in the context of a meta-analysis supplementing a systematic review. In the process, the central question was to statistically determine whether, and to what extent, nucleoplasty can positively affect pain relief and functional mobility as well as lower the complication rate.

Objective: Newly published studies made it possible to conduct a meta-analysis of the visual analog scale (VAS), a measuring instrument used to determine pain intensity, and the Oswestry Disability Index (ODI), a scale that reflects the degree of impairment in percent. In addition to having clearly sound evidence for analyzing VAS/NPS data, the present, newly compiled meta-analysis was able to summarize VAS and ODI data quantitatively and to calculate a total complication rate for the first time. It was thereby possible to make a first comparison between nucleoplasty and conservative therapy (including epidural steroid injection).

Study Design: This meta-analysis examined all study data published in clinical trials involving the nucleoplasty procedure for plasma disc decompression.

Methods: A systematic search using the terms nucleoplasty and/or plasma disc decompression was conducted for literature listed in MEDLINE. Twenty-seven eligible studies (22 prospective trials and 5 retrospective trials) were included, and pooled analyses as well as various subgroup analyses (differentiation between cervical and lumbar disc herniations, comparisons with alternative treatments such as epidural steroid injection) were performed based on their data.

Results: Pain decreased from a baseline VAS value of 7.27 to 2.12 (postop/first day), 2.50 (one week), 2.70 (2 weeks), 3.23 (one month), 2.66 (6 weeks), 2.84 (3 months), 3.06 (6 months), 3.03 (12 months), 1.54 (18 months), and 3.69 (24 months) after nucleoplasty. The ODI value (baseline: 58.95) dropped to 28.60 (one week), 29.00 (2 weeks), 23.21 (one month), 30.00 (6 weeks), 18.30 (3 months), 22.54 (6 months), 24.43 (12 months), 12.82 (18 months), and 36.98 (24 months). Compared to baseline, significant pain reduction and improvement in functional mobility after nucleoplasty were observed at every time point. Nucleoplasty showed a total complication rate of 1.5%, with the individual rates being 0.8% for cervical and 1.8% for lumbar nucleoplasty. Nucleoplasty was superior to conservative therapy at every time point and for all 3 included parameters, at some measurement time points even significantly.

Conclusions: Nucleoplasty reduces pain in the long term and improves patients' functional mobility. It is an effective, low-complication, minimally invasive procedure used to treat disc herniations.

Key words: Nucleoplasty, plasma disc decompression, (contained) herniated discs, visual analog scale (VAS), numeric pain scale (NPS), complication rate, Oswestry Disability Index (ODI), pain reduction

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Low back pain is defined as pain in the back beneath the costal arch and above the natal clefts, with or without radiation (1).

Low back pain is one of the most frequently occurring types of pain (1). According to one investigation conducted in the Federal Republic of Germany, the point prevalence for back pain was 37.1%, one-year prevalence was 76.0%, and life-time prevalence was 85.5%. Prevalence declined as the level of education increased; some even regard education as the most important predictor for the occurrence of back pain (2). It appears certain that a person's social status (as measured by their education, occupation, and income) is related to the risk of back pain (3). People of low social status reported back pain in general and severe back pain in particular much more often compared to those having a high socioeconomic status (4).

Corresponding with these findings are work-related circumstances linked to the risk for back pain, particularly biomechanical working conditions (e.g., carrying and lifting of heavy loads), vibrations, and unfavorable body postures while working (5). Contrary to popular belief, however, it appears that predominantly sedentary work poses no significant risk for low back pain (6).

Results similar to those observed in Germany can also be found in the USA: 26.4% of the American adult population reported having had back pain that lasted at least one day within the past 3 months. According to this study, too, the prevalence of back pain decreased as education levels and incomes increased (7).

Back pain occurs both in industrialized and developing countries. Overall, up to one-half of the working population experiences an episode of back pain at least once a year. Hence, back pain represents a leading cause of absence from work and results in considerable economic loss (8). Based upon this finding, it is said that a worldwide yearly equivalent of 800,000 DALYs (disability-adjusted life year = measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death [9]) is lost. Up to 40% of cases of back pain are attributed to occupational stress; a preventive approach can therefore take place in this area (8).

It is estimated that in the USA alone at least 116 million adults suffer from chronic pain, incurring annual costs of 560 to 635 billion US dollars resulting from medical treatment and production losses (10).

Thus, in the US health care system the annual costs of pain were higher than expenses for heart disease, cancer, and diabetes (11). As for the European Union, one assumes that the extrapolated total costs of chronic pain amount to 300 billion euros (Am. Engl.), corresponding to about 1.5 – 3% of the GDP (12).

The treatment of back pain, which originates in the spinal region, differs considerably depending on the procedure applied:

Current, evidence-based guidelines on interventional techniques suitable for treating chronic back pain recommend epidural steroid injection in cases of cervical and lumbar disc herniations (13). Furthermore, spinal nerve analgesia and epidural-neuronal injection therapy for treating nerve root compression syndromes constitute a substantial part of conservative therapy (14).

A large randomized study involving over 1,200 patients in the USA who were observed for 4 years, however, demonstrated the superiority of surgical standard laminectomy to conservative therapy (in the study not including epidural steroid injection) for lumbar disc herniations (15).

The absolute indications for discectomy are the paralysis of functionally important muscles or cauda equina syndrome. Severe pain conditions are also considered an indication; however, further specification is lacking. Low back pain only, without radicular symptoms and despite proven disc protrusion, even constitutes a contraindication (16). The range of indications for surgery is thus extremely small and does not include most patients with disc herniations.

Nucleoplasty could possibly close the gap between the various established procedures used to treat back pain. Evidence in favor of nucleoplasty as a relatively new procedure, however, is only described as limited to fair in the current guidelines on interventional techniques for treating chronic back pain (13).

A systematic review by Gerges et al (17) appeared in March 2010 with the title "A Systematic Review on the Effectiveness of the Nucleoplasty Procedure for Discogenic Pain." This review analyzed literature published through September 2008. The investigation mainly focused on the evaluation of pain intensity using visual analog scale / numeric pain scale (VAS/NPS) values. The evaluation of functional capacity in the meta-analysis by Gerges et al (17) is based upon 3 studies, each conducted by the same author (18-20) and using the author's own score. Gerges et al (17) pointed out the insufficient amount of data from the 14 studies—only one of which was randomized—that were included in their meta-analysis.

In January 2013, a brief systematic review appeared that only included randomized, controlled studies on nucleoplasty applied in patients with disc herniations (21).

Thereafter, a systematic review with the title "An Update of the Systematic Assessment of Mechanical Lumbar Disc Decompression with Nucleoplasty" by Manchikanti et al (22) was published in April 2013, which represents an update of the same authors' article that had appeared in 2009 (23). The review took literature published through September 2012 into consideration. Primary outcome parameters were pain relief and functional improvement, assessed according to the various scores used in the studies chosen for the review. This article, too, concluded that the evidence favoring nucleoplasty was limited to fair, but on no account was it good.

From October 2008 to September 2012, however, over a dozen new clinical studies investigating nucleoplasty appeared, many of which again used the VAS value, among others, as an outcome parameter. Manchikanti et al (22) did in fact evaluate these new clinical studies in the context of their systematic review on nucleoplasty; still lacking overall, however, is a meta-analysis supplementing the systematic review that summarizes and interprets the reported results, where possible comprehensively and quantitatively, with the help of statistical methods. Compared to systematic reviews, which are characterized methodically in particular by a detailed study protocol and analysis plan as well as a literature search for suitable studies in accordance with a priori defined inclusion and exclusion criteria, a meta-analysis also provides a quantitative, statistical summary of the results (24).

This paper therefore aimed to improve the scientific evidence on nucleoplasty even further by conducting a supplemental comprehensive meta-analysis. In short, the present meta-analysis deals with the central question of the extent to which it is statistically proven that the nucleoplasty treatment method can positively affect pain relief and functional mobility and lower the complication rate.

The new studies published since October 2008 have made it possible to conduct a meta-analysis of the VAS, a measuring instrument for determining pain intensity (25), and of the Oswestry Disability Index (ODI), a scale that reflects the degree of impairment in terms of percent (26). The present, newly conducted meta-analysis thus quantitatively summarizes VAS and ODI data as well as calculates a total complication rate, which previous systematic reviews were unable to illustrate quantitatively or graphically.

Methods

In short, it was the intent of the current meta-analysis to answer the question as to the degree to which the nucleoplasty treatment procedure can have a positive effect on pain relief and functional mobility as well as lower the complication rate.

Search Strategy and Selection Criteria

A systematic search using the terms "nucleoplasty" and/or "plasma disc decompression" was conducted in the MEDLINE database.

Literature published up to and including September 30, 2012, was included.

The inclusion criteria for the meta-analysis were:

1. treatment with nucleoplasty for intervertebral disc conditions
2. publications in English (27)
3. clinical studies with patient populations at defined measurement time points
4. at least 2 or more points on the modified Jadad scale

Outcome parameters to be considered:

VAS/NPS

The VAS is a standardized instrument for measuring pain. Patients rate the intensity of their subjectively experienced pain on a 10 cm scale from 0 (no pain) to 10 (greatest imaginable pain) with a space of one centimeter between the individual values (25).

Complication rate

The complication rate, specified in percent, describes all adverse events occurring in a patient population.

ODI

The ODI, developed by Fairbanks et al in 1980, is a 10-item patient-based questionnaire used to make a standardized assessment of functional restriction in spinal mobility caused by back pain (low back pain disability), where minimal impairment is rated with 0 points and maximal impairment 100 points (26).

Complete statistical data sets consisting of sample size, mean, and standard deviation (if appropriate,

calculation using standard error or the upper and lower quartile) at defined follow-up time points.

Data Collection and Analysis

Seventy-six articles were identified using the term "nucleoplasty" and 10 publications using "plasma disc decompression." Two papers (28,29) contained both search terms, resulting in a total of 86 studies using both search terms.

Additional literature was found while examining the bibliographies of these 86 articles. It was therefore possible to make a primary evaluation of a total of 125 articles based on their abstracts. We proceeded as follows:

An initial review of the 125 abstracts revealed that 45 articles were not primarily concerned with nucleoplasty, but instead reported on other treatment options for intervertebral disc conditions or only mentioned "nucleoplasty" (30-74).

Therefore, a remaining 80 articles were analyzed. Another 35 of these were excluded because they involved reviews and meta-analyses (18x) (17,23,75-90), basic research (10x) (91-100), guidelines (3x) (101-103), or comments (1x) (104) and not clinical studies with patient case numbers. Also excluded were a case report by Li et al on hemophilia in a patient following nucleoplasty (105), one case report by Zhu et al using nucleoplasty for segment degeneration after fusion surgery (106), and one study by Cuellar et al on failed nucleoplasty (107). All of these articles, upon considering the inclusion criteria, did not address nucleoplasty for intervertebral disc conditions.

At the beginning, we therefore found 45 studies which reported on the clinical application of nucleoplasty. Of these, another 18 studies were excluded for the following reasons:

Even though the patients in the study conducted by Li et al (108) underwent nucleoplasty, the study had to be excluded because the indication was discitis and not disc herniation.

The study by Fabrizi et al (109) could not be included, in which a Coblation-assisted microdiscectomy was performed. Coblation is in fact the underlying technical procedure of nucleoplasty, but it is not usually used in microdiscectomies.

Also, the paper by Theron et al (110) could not be considered since the study addressed the use of "radiopaque gelified ethanol," and nucleoplasty was only applied in addition to this procedure in a subgroup of 11 patients. The study results are therefore not exclusively attributable to nucleoplasty.

The articles by Li et al (111), Zakirov et al (112), and Manukovskii et al (113) were published only in Chinese or Russian and were eliminated in accordance with the inclusion criteria. Furthermore, the studies by Cohen et al (114) and Yan et al (115) were not taken into consideration, since they did not specify any precisely defined measurement time points (only mean values of 9 and 29 months, respectively, were mentioned).

The article by Bokov et al (116) described the follow-up period and the patient population of a patient cohort already considered in the meta-analysis (117) and was therefore not included twice.

The 3 case reports by Singh (118), Smuck et al (119), and Puentedura et al (120) as well as the 2 case report series by Pace et al (121) and Chua et al (122) were excluded based on their low level of evidence (123).

The papers by Reverberi et al (124) and Al-Zain et al (125) could not be considered at all for the meta-analysis due to lacking standard deviations for VAS and ODI values, respectively.

To be able to establish the homogeneity essential for a meta-analysis, we set a minimal score of at least 2 points on the modified Jadad scale. Two studies, one by Wolter et al (126) and the other by Bonaldi et al (127), thus dropped out because they only reached a score of one on the modified Jadad scale. The Jadad scale was presented by Jadad et al in Oxford (therefore also called the Oxford scale) in 1996 for making a qualitative assessment of the methodology of studies conducted in pain research. Originally, the Jadad scale consisted of 3 questions pertaining to randomization, blinding, and study dropouts in pain studies (128).

In 2001, Oremus et al added to the original Jadad scale 3 more questions regarding inclusion and exclusion criteria, side effects/negative effects, and statistical methods. Furthermore, one additional point each was given for adequate randomization and blinding, resulting in a total minimal score of 0 and a maximal score of 8 (129).

This meta-analysis implemented the Jadad scale as adapted by Oremus. In order for no systematic error to be made in this meta-analysis, a second, blinded reviewer applied the scale to assess all studies. If the second reviewer reached a different evaluation of a study, a third reviewer was consulted to assess the study in question.

Fig. 1 presents a flowchart of the procedure followed in selecting literature for this meta-analysis and thus in identifying relevant literature for this meta-analysis.

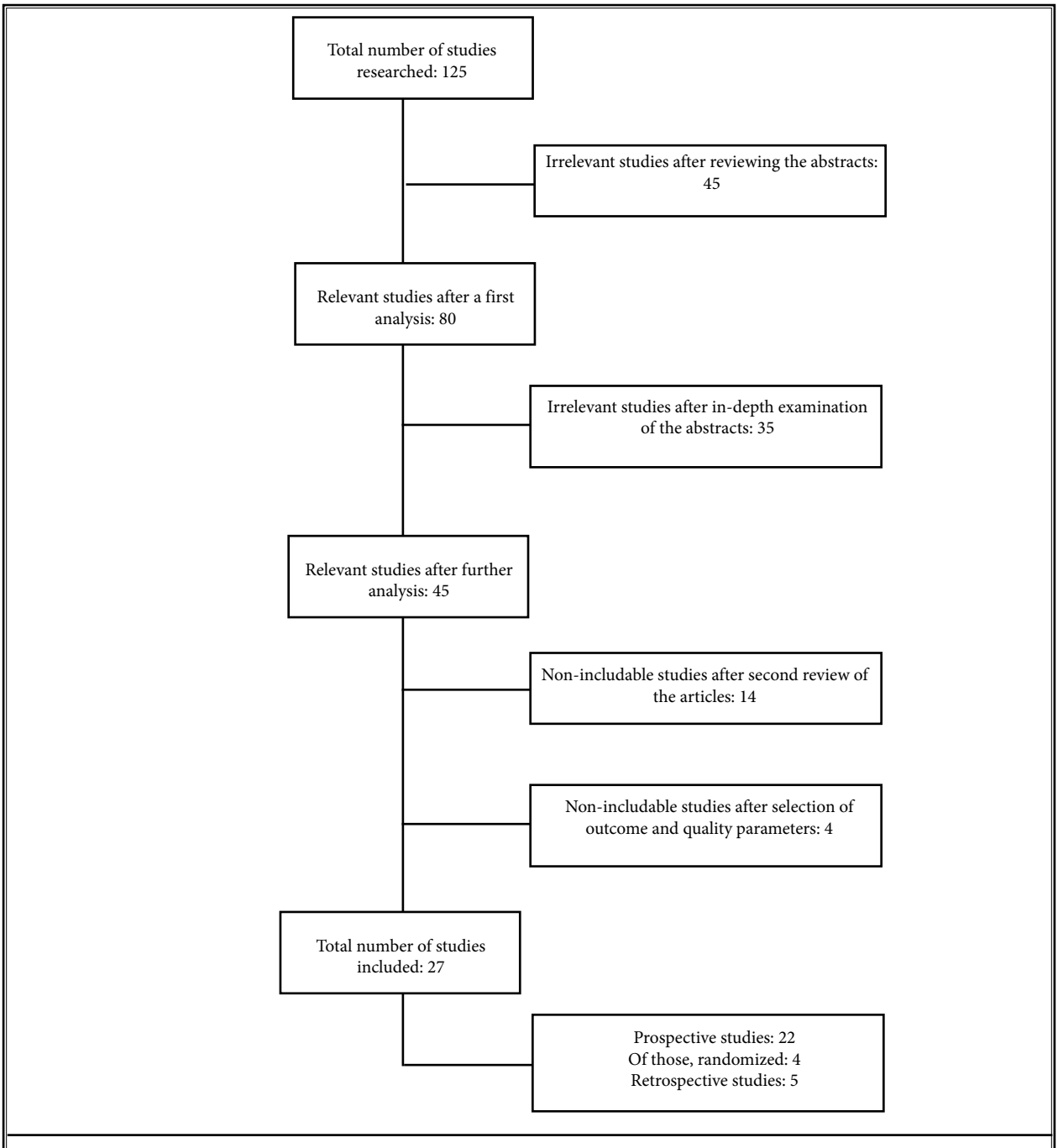

Fig. 1. *Flowchart: Identification of relevant studies.*

Taking the defined outcome and quality parameters into account, it was possible to include 27 studies this meta-analysis (Table 1).

At first, study values were listed in a table. In the event that no change in the patient number was specified in the observation period of a study, the number of patients treated at baseline was used for calculation purposes.

Based on the sample sizes and the study values reported in the studies, we performed the statistical calculations using the statistics software called "Com-

Table 1. *Salient features of studies included.*

Author	Study design	Follow-up	Patients treated with nucleoplasty	VAS/ NPS	CR	ODI	Segment
Alexandre et al (130)	prospective, non-randomized, non-controlled	12 months	1,390		X		lumbar
Azzazi et al (131)	prospective, non-randomized, non-controlled	12 months	50	X	X	X	lumbar
Bhagia et al (132)	prospective, non-randomized, non-controlled	2 weeks	53	X	X		lumbar
Birnbaum (28)	prospective, randomized, controlled	24 months	29 / 30 conservative therapy	(X)	X		cervical
Bokov et al (117)	prospective, non-randomized, controlled	18 months	73 / 65 microdiscectomy	X	X	X	lumbar
Calisaneller et al (133)	prospective, non-randomized, non-controlled	6 months	29	X	X		lumbar
Cesaroni & Nardi (134)	prospective, randomized, controlled	12 months	62 / 53 conservative therapy	X	X		cervical
Cesaroni & Nardi (135)	retrospective, non-randomized, non-controlled	5 years	349		X		cervical
Gerszten et al (136)	prospective, randomized, controlled	24 months	45 / 40 transforaminal epidural steroid injection	X	X	X	lumbar
Gerszten et al (137)	prospective, non-randomized, non-controlled	6 months	67	(X)	X		lumbar
Karaman et al (138)	prospective, non-randomized, non-controlled	24 months	56	X	X	X	lumbar
Lemcke et al (139)	prospective, non-randomized, controlled	12 months	96 / 67 Disc Dekompressor	X			lumbar
Li et al (140)	prospective, non-randomized, non-controlled	12 months	126	X	X		cervical
Marin (29)	prospective, non-randomized, controlled	12 months	64 / 13 Coblation-assisted microdiscectomy	(X)	X		lumbar
Masala et al (141)	prospective, non-randomized, non-controlled	12 months	72	(X)	X		lumbar
Mirzai et al (142)	prospective, non-randomized, non-controlled	12 months	52	X	X	X	lumbar
Nardi et al (143)	prospective, randomized, controlled	2 months	50 / 20 conservative therapy	(X)	X		cervical
Reddy et al (144)	retrospective, non-randomized, non-controlled	12 months	49	(X)	X		lumbar / thoracic
Shabat et al (145)	prospective, non-randomized, non-controlled	24 months	87	(X)	X	(X)	lumbar
Sharps & Isaac (146)	prospective, non-randomized, non-controlled	12 months	49	X	X		lumbar
Sim et al (147)	retrospective, non-randomized, non-controlled	6 months	22	X	X		cervical
Sinan et al (148)	prospective, non-randomized, non-controlled	12 months	83	(X)	X		lumbar
Singh et al (20)	prospective, non-randomized, non-controlled	12 months	47	X	X		lumbar
Singh et al (19)	prospective, non-randomized, non-controlled	12 months	80	X	X		lumbar
Singh et al (18)	prospective, non-randomized, non-controlled	12 months	67	X	X		lumbar
Yakovlev et al (149)	retrospective, non-randomized, non-controlled	12 months	22	X	X		lumbar
Zhu et al (150)	retrospective, non-randomized, non-controlled	24 months	42	X		X	lumbar

CR = complication rate, (X) = non-includable/non-evaluable study parameters.

prehensive Meta-Analysis" (Version 2.2.057; 9 December 2010; Biostat, 14 North Dean Street, Englewood, NY, 07631, USA).

The study values for the outcome parameters VAS, complication rate, and ODI were sorted according to measurement time points (for example: baseline, post-OP, one week, one month, etc.) and summarized using a random-effects model.

P-values for comparison of groups (for example: nucleoplasty versus conservative therapy) were calcu-

Table 2. *Systematic presentation of the studies used.*

Author	Jada total	Average age	Age span	Measurement time points	Inclusion criteria	Exclusion criteria
Alexandre et al (130)	2	not specified	not specified	preoperative, 15 days, 1, 6, and 12 months after nucleoplasty with 1,390 patients	chronic lumbar pain with or without radicular pain lasting more than 3 months absence of neurological deficit one level positive provocative discography	disc herniation with sequestration large contained herniation that was larger than one- third the sagittal diameter of the spinal canal severe spinal stenosis presence of secondary pain issues psychological disorders gait disorders depending on different neurological or orthopedic pathology
Azzazi et al (131)	4	41	25 – 61	preoperative, 2 weeks, 1, 3, 6, 12 months after nucleoplasty with 50 patients	disc protrusion or contained herniated disc < 6 mm with a disc height > 50% of the adjacent disc heights	previous lumbar surgery significant spinal stenosis motor weakness fracture, tumor, spondylolisthesis more than 2 symptomatic levels
Bhagia et al (132)	4	42.1	17 – 78	preoperative, 2 weeks after nucleoplasty with 53 and 49 patients	contained disc herniation with a disc height > 50% of the adjacent disc heights presence of discogenic axial back pain or leg pain	sequestered disc large contained herniation that was larger than one third the sagittal diameter of the spinal canal presence of progressive neurologic deficits spinal instability, fracture, tumor, morbid obesity, infection spondylolisthesis marked spinal stenosis due to extensive osteophytosis all patients with axial back pain without radicular symptoms underwent provocative discography to confirm concordant pain
Birnbaum (28)	3	not specified	23 – 49	preoperative, 1 day, 1 week, and 1, 3, 6, 12, and 24 months after nucleoplasty with 29, 29, 29, 29, 29, 29, 29, and 26 patients	arm pain > back pain contained disc protrusion or contained herniated disc not larger than 4 mm and not compromising more than one-fourth of the central spinal canal	disc height < 50% of the adjacent disc heights evidence of severe disc degeneration fracture, tumor moderate/severe spinal stenosis
Bokov et al (117)	3	43.0	not specified	preoperative, 1, 3, 6, 12, and 18 months after nucleoplasty with 73 patients	evidence of nerve root compression with VAS > 4 and ODI > 40	litigation uncontrolled psychological disorders evidence of instability of the segment infection severe and progressive neurological deficit previous spinal surgery spinal stenosis
Calisaneller et al (133)	3	44.14	32 – 59	preoperative, 1 day, 3, and 6 months after nucleoplasty with 29 patients	low back pain and/or leg pain lasting more than 6 months diffuse bulging and/or protrusion < 5 mm at one or 2 levels	disc bulges greater than 5 mm loss of normal disc height greater than 30% previous low-back surgery, neurological deficits serious medical conditions such as malignancy, infection or coagulopathy
Cesaroni & Nardi (134)	6	45.03	18 – 75	preoperative ,6 weeks, 3, 6, and 12 months after nucleoplasty with 62, 62, 62, 61, and 61 patients	neck/arm pain VAS > 5 single contained symptomatic focal disc protrusion between C3 and T1 not compromising more than one-third of the central spinal canal minimal corroborative myotomal deficit a positive diagnostic nerve root block failed to respond to or refused epidural steroid injection	extruded or sequestered disc larger than 6 mm with a disc height < 50% of the adjacent disc heights disc prolapse that was larger than one-third the sagittal diameter of the spinal canal history of anterior fusion in the cervical level to be treated fracture, tumor, infection central cord lesion in the cervical spine progressive neurological deficit hyperostosis causing concurrent foraminal stenosis at the symptomatic level myotomal deficit with motor strength less than 4/5 carotid stenosis or significant plaque-like carotid disease

Table 2 (cont.). *Systematic presentation of the studies used.*

Author	Jada total	Average age	Age span	Measurement time points	Inclusion criteria	Exclusion criteria
Cesaroni & Nardi (135)	2	not specified	not specified	preoperative, 12, 24, 36, 48, and 60 month after nucleoplasty with 349, 302, 190, 170, 124, and 69 patients	disc protrusion < 3mm not compromising more than one-fifth of the central spinal canal	fracture, tumors acquired stenosis advanced spondylosis resulting in osseous foraminal stenosis or disc space collapse previous spinal surgery neurological deficit as hypoesthesia or motor deficits
Gerszten et al (136)	6	46	20 – 66	preoperative, 1, 3, and 6 months after nucleoplasty with 45, 40, 30, and 29 patients (12 and 24 months not reported)	lumbar disc protrusion with radicular pain score > 5 and with a disc height > 50% of the adjacent disc heights BMI less than 40	sciatica originating from more than one disc level back pain more than leg pain cauda equina syndrome progressive neurological deficit spondylolisthesis or moderate or severe stenosis at the level to be treated previous spinal surgery at or directly adjacent to the level to be treated fracture, tumor, infection
Gerszten et al (137)	3	41	21 – 70	preoperative, 3, and 6 months after nucleoplasty 67, 34, and 23 patients	leg pain > back pain contained disc protrusion with a disc height > 75% of the adjacent disc heights discography positive for concordant pain	complete anular disruption with extruded or sequestered disc disc height < 25% of adjacent level(s) moderate to severe spinal stenosis fracture, tumor, infection
Karaman et al (138)	3	40	18 – 59	preoperative, 1, 6, 12, and 24 months after nucleoplasty with 56, 56, 54, 52. and 50 patients	younger than 60 years contained single level disc herniation < 6mm with mostly single-side leg pain with a disc height > 70% of the adjacent disc heights disc prolapse that was smaller than one third the sagittal diameter of the spinal canal	extruded or sequestered disc larger than 6 mm back pain more than leg pain previous open surgery or percutaneous intervention on PN planned level more than one herniation with different levels instability, tumor, spondylolisthesis presence of general contraindications, such as bleeding diathesis, known allergy history for materials used, psychological disorder, or systemic infection or local infection in the intervention area
Lemcke et al (139)	3	42	18 – 74	preoperative, postOP/one day, 6, and 12 months after nucleoplasty with 96, 96, 77, and 69 patients	contained disc herniation (disc bulging or disc protrusion) low back pain and/or persisting pain radiating to the lower extremities	extruded or sequestered disc disc prolapse that was larger than one third the sagittal diameter of the spinal canal previously operated segments severe neurological deficits co-existing neoplastic or infectious disease
Li et al (140)	3	51.9	34 – 66	preoperative, 2, weeks, 1, 3, 6, and 12 months after nucleoplasty with 126 patients	contained disc herniation complaints of radicular pain with or without neck pain	sequestered herniation hemorrhagic diasthesis spondylolisthesis spinal canal stenosis ossification of longitudinal ligament (OPLL) previous surgery at the indicated level myelopathy
Marin (29)	3	43	23 – 57	preoperative, 1, 3, 6, 9, and 12 months after nucleoplasty with 64, 62, 58, 47, 35, and 15 patients	back pain with or without radicular pain disc protrusion having a disc height > 30% with radicular/axial pain	sequestered disc previous spinal surgery disc prolapse that was larger than one third the sagittal diameter of the spinal canal severe spinal stenosis progressive neurological deficits
Masala et al (141)	4	48	32 – 64	preoperative and 12 months after nucleoplasty with 72 and 70 patients	lumbalgic and/or sciatalgic pain due to disc protrusions and contained herniations absence of major neurologic deficit	secondary gain issues, litigation heavy opioid usage uncontrolled psychological disorders extruded or sequestered disc contained herniation that was larger than one-third the sagittal diameter of the spinal canal severe degenerative disk with greater than 33% loss of disk height non-qualifying results on provocative discography marked spinal stenosis due to extensive osteophytosis previous spinal surgery in the same region spondylolisthesis, bone congenital abnormalities spinal instability, infection, tumor, cauda equina syndrome

Table 2 (cont.). *Systematic presentation of the studies used.*

Author	Jada total	Average age	Age span	Measurement time points	Inclusion criteria	Exclusion criteria
Mirzai et al (142)	3	44.8	not specified	preoperative, 2, weeks, 6, and 12 months after nucleoplasty with 52, 50, 50, and 47 patients	contained disc herniation < 6mm with a disc height > 50% of the adjacent disc heights radicular pain	large (> 6 mm) or extruded disc herniation severe degenerative disc material or complete annular disruption significant spinal stenosis older than 60 years fracture, tumor, spondylolisthesis disc height < 50%, back pain greater than leg pain
Nardi et al (143)	4	not specified	not specified	preoperative, 1 day, 1 week, and 2 months after nucleoplasty, with 50 patients	disc protrusion < 3mm not compromising more than one-fifth of the central spinal canal persistent cervical or unilateral arm pain	acquired stenosis previous spinal surgery fracture, tumor neurological deficit as hypoesthesia or motor deficits advanced spondylosis resulting in osseous foraminal stenosis or disc space collapse
Reddy et al (144)	3	45	22 – 67	preoperative, 6, and 12 months after nucleoplasty with 49 patients	Radicular criteria leg pain > back pain contained posterior disc protrusion positive discography with concordant pain or failed selective nerve root block Axial criteria contained central focal disc protrusion or positive discography with concordant pain	a loss of more than 50% of disc height moderate to severe spinal stenosis evidence of severe disc degeneration fracture, tumor
Shabat et al (145)	4	49	22 – 67	preoperative, 1, 3, 6, 12, and 24 months after nucleoplasty with 87, 87, 87, 87, 85, and 39 patients	contained disc herniation (up to 2 levels) with a disc height > 50% of the adjacent disc heights radicular low back pain with or without mechanical low back pain	sequestered herniation instability such as spondylolisthesis or spondylolysis
Sharps & Isaac (146)	3	38	30 – 61	preoperative, 1, 3, 6, and 12 months after nucleoplasty with 49, 49, 41, 24, and 13 patients	complaints of back with or without radicular pain	sequestered herniation contained herniation that was larger than one-third the sagittal diameter of the spinal canal spinal stenosis presence of progressive neurological deficits spinal fracture, tumor, infection participation in any other drug or device study
Sim et al (147)	2	47.8	19 – 71	preoperative, 1, and 6 months after nucleoplasty with 22 patients	not specified	not specified
Sinan et al (148)	3	not specified	20 – 64	preoperative, 1 week, 1, 3, 6, 9, and 12 months after nucleoplasty with 83 patients	symptoms of disc protrusion with a disc height > 50% of the adjacent disc heights	extruded or sequestered disc previous spinal surgery severe neurological deficits instability of the segment, tumor, infection serious medical conditions
Singh et al (20)	4	44	15 – 62	preoperative, 1, 3, 6, and 12 months after nucleoplasty with 47, 46, 42, 40, and 37 patients	discogenic low back pain confirmed by discography with concordant pain VAS > 5 absence of neurologic deficit	litigation heavy opioid usage uncontrolled psychological disorders disc herniation with sequestration contained herniation that was larger than one-third the sagittal diameter of the spinal canal non-qualifying results on provocative discography, spinal instability, infection marked spinal stenosis due to extensive osteophytosis

Table 2 (cont.). Systematic presentation of the studies used.

Author	Jada total	Average age	Age span	Measurement time points	Inclusion criteria	Exclusion criteria
Singh et al (19)	4	44.8	15 – 62	preoperative, 1, 3, 6, and 12 months after nucleoplasty with 80, 79, 75, 72, and 62 patients	discogenic low back pain and/or leg pain for 3 or more months confirmed by discography with concordant pain absence of neurologic deficit	secondary gain issues heavy opioid usage uncontrolled psychological disorders disc herniation with sequestration contained herniation that was larger than one third the sagittal diameter of the spinal canal infection marked spinal stenosis due to extensive osteophytosis equivocal discography results
Singh et al (18)	4	44	15 – 62	preoperative, 1, 3, 6, and 12 months after nucleoplasty with 67, 66, 62, 61, and 41 patients	contained disc herniation with presence of discogenic axial back pain and/or leg pain positive provocative discography with elicitation of concordant pain and at least one negative control disc absence of neurologic deficit	litigation heavy opioid usage disc herniation with sequestration contained herniation that was larger than one-third the sagittal diameter of the spinal canal uncontrolled psychological disorders non-qualifying results on provocative discography spinal instability, infection marked spinal stenosis due to extensive osteophytosis
Yakovlev et al (149)	4	39	22 – 51	preoperative, 1, 3, 6, and 12 months after nucleoplasty with 22 patients	contained disc protrusion with a disc height > 50% of the adjacent disc heights discography confirming concordant pain at each suspected level and ruling out involvement at other levels radicular or axial low back pain of 6 or more months absence of neurologic deficit	disc sequestration spinal stenosis more than 2 symptomatic levels history of open disk surgery at suspected levels fracture, infection, tumor prominent coexisting psychological disorders
Zhu et al (150)	2	39.8	21 – 56	preoperative, 1 week, 12, and 24 months after nucleoplasty with 42 patients	contained disc protrusion with a disc height > 50% of the adjacent disc heights discogenic low back pain discography confirming concordant pain at each suspected level	disc protrusion that was larger than one-third the sagittal diameter of the spinal canal spinal stenosis previously operated segments severe neurological deficits spinal tumors infectious diseases

Table 3. *Systematic presentation of perioperative data from the studies used.*

Author	**Pre-operative diagnostics**	**Prior treatment**	**Perioperative antibiotics**	**Anesthesia**	**Additional treatment directly after nucleoplasty**	**Additional outcome parameters**
Alexandre et al (130)	MRI/CT	3 months of conservative therapy	none	intravenous sedation	none	MRI/CT, JOA Score Scale
Azzazi et al (131)	MRI	3 months of conservative therapy	prophylactic intravenous antibiotic	local anesthesia or monitored anesthesia	none	Analgesic consumption, MRI/CT
Bhagia et al (132)	not specified	6 weeks of conservative therapy including epidural steroid injections for axial pain, selective nerve root injections for radicular pain	none	not specified	2.0 mL betamethasone or Depo-Medrol and 1.0 mL of 1.0% Xylocaine for radicular symptoms	not specified
Birnbaum (28)	MRI	2 – 3 months of conservative therapy including epidural steroid injections and selective nerve root blocks	2g cefazolin	local anesthesia and under analgosedatives	none	not specified
Bokov et al (117)	MRI, optional CT	conservative therapy including selective nerve root blocks	none	intravenous sedation	betamethasone and lidocaine	not specified

Table 3 (cont.). *Systematic presentation of perioperative data from the studies used.*

Author	Pre-operative diagnostics	Prior treatment	Perioperative antibiotics	Anesthesia	Additional treatment directly after nucleoplasty	Additional outcome parameters
Calisaneller et al (133)	MRI	6 weeks of conservative therapy	none	local anesthesia	none	MRI/CT
Cesaroni & Nardi (134)	MRI	30 days of conservative therapy	cephalosporin	intravenous sedation	none	not specified
Cesaroni & Nardi (135)	not specified	conservative therapy	cephalosporin	intravenous sedation	none	SF 36 (36-Item Short Form Health Survey), NDI (Neck Disability Index)
Gerszten et al (136)	not specified	epidural steroid injections	none	not specified	none	satisfaction with treatment, SF 36 (36-Item Short Form Health Survey)
Gerszten et al (137)	MRI	6 weeks of conservative therapy	none	local anesthetic or induction of general anesthesia	none	SF 36 (36-Item Short Form Health Survey), EQ 5D (EuroQol 5D)
Karaman et al (138)	MRI	conservative therapy at least for 6 weeks within the last 6 months	1 g cefazolin	local anesthesia	none	satisfaction with treatment
Lemcke et al (139)	MRI	6 weeks of conservative therapy	1.5 g cefazolin	local anesthesia	none	analgesic consumption, ability to work, disability in daily life
Li et al (140)	MRI and CT	6 weeks of conservative therapy	not clear defined	local anesthesia	none	Macnab criteria, segment stability
Marin (29)	MRI	6 weeks of conservative therapy	1 g cefazolin	local anesthesia and intravenous sedation	none	analgesic consumption, satisfaction with treatment, return to work
Masala et al (141)	MRI	6 weeks of conservative therapy	none	intravenous sedation	none	satisfaction with treatment, MRI/CT
Mirzai et al (142)	MRI	3 months of conservative therapy	none	local anesthesia	none	analgesic consumption, satisfaction with treatment
Nardi et al (143)	MRI	conservative therapy	cephalosporin	intravenous sedation	none	MRI/CT
Reddy et al (144)	MRI	3 months of conservative therapy	1 g cefazolin	local anesthesia and intravenous sedation	5 cc (=mL) 0.25% bupivacaine und 60 mg methylprednisolone	analgesic consumption, satisfaction with treatment, work & leisure impairment
Shabat et al (145)	MRI/CT	6 months of conservative therapy including epidural steroid injections	1 g Cefamyzin i.v.	local anesthesia	none	not specified
Sharps & Isaac (146)	not specified	6 weeks of conservative therapy (including epidural steroid injections for radicular symptoms)	1 gm of intravenous cefazolin and 500 mg of oral Cephalexin every 6 hours for 48 hours. Patients with penicillin or cephalosporin allergy: 400 mg of intravenous ciprofloxacin prior to the procedure and 500 mg orally twice a day for 48 hours.	local anesthesia	none	analgesic consumption, satisfaction with treatment, return to work

Table 3 (cont.). *Systematic presentation of perioperative data from the studies used.*

Author	Pre-operative diagnostics	Prior treatment	Perioperative antibiotics	Anesthesia	Additional treatment directly after nucleoplasty	Additional outcome parameters
Sim et al (147)	MRI	not specified	1 g cefazolin	local anesthesia and on-demand intravenous sedation	none	Macnab criteria
Sinan et al (148)	MRI	2 weeks of conservative therapy partially including epidural steroid injections	none	intravenous sedation	none	RMDQ
Singh et al (20)	not specified	3 months or more of conservative therapy including injection therapy	intradiscal or intravenous antibiotics	intravenous sedation	none	functional improvement
Singh et al (19)	not specified	3 months or more of conservative therapy including injection therapy	none	monitored anesthesia	none	functional improvement
Singh et al (18)	not specified	3 months or more of conservative therapy including injection therapy	none	local anesthesia and monitored anesthesia	none	functional improvement
Yakovlev et al (149)	MRI	conservative therapy including epidural steroid injections and selective nerve root injections	40mg cefazolin (local)	monitored anesthesia	2mL 0.25% bupivacaine	analgesic consumption, return to work, functional status
Zhu et al (150)	MRI	6 months of conservative therapy	1.5 g cefazolin	local anesthesia	For patients with radicular symptoms, 2.0 mL of betamethasone and 1.0 mL of 1.0% lidocaine	not specified

lated with Z-Statistik software.

The 27 studies we used were compiled in 2 tables in the context of this systematic review (Tables 2 and 3).

VAS

If in a study several numerical VAS/NPS figures were found because various pain intensities had been documented for various body regions of the patients, the arithmetic mean was calculated to harmonize the VAS/NPS data for "back pain" and "leg/radicular pain."

This step was necessary to calculate a total value for one measurement time point defined in the respective studies by Bhagia et al (132), Gerszten et al (136), Lemcke et al (139), and Zhu et al (150).

The VAS values for "numbness" from the study by Zhu et al (150) were the only values not included in the calculation, since they clearly did not involve pain assessments.

The paper by Bhagia et al (132) was taken into consideration. Although no standard deviation was indicated for the defined measurement time point, the standard deviation of the change in VAS was indeed specified. This standard deviation was able to be applied for the baseline value assuming a correlation of 0.5 between the baseline and the 2-week values. This decision was based on the "Cochrane Handbook for Systematic Reviews for Interventions" (151).

Furthermore, it was possible to include the article by Singh et al (19) published in 2003 in the meta-analysis. The missing standard deviation for the baseline value was able to be taken from the article by Singh et al (18) from 2002 in accordance with the "Cochrane Handbook for Systematic Reviews for Interventions" (151); in general, both studies reported strikingly similar values.

The data reported by Bokov et al (117) in the nucleoplasty group had to be calculated separately, because in this study 3 differently sized subgroups having patients with differently sized disc herniations had undergone nucleoplasty. Based on the respective group size, we were able to calculate the proportion of single values with respect to the new total value.

Due to missing standard deviations for VAS values, we could not include the paper by Birnbaum (28) in the VAS calculation. The same applies to the articles by Gerszten et al (137), Masala et al (141), Shabat et al (145), and Sinan et al (148).

The papers by Marin (29), Nardi et al. (143), and Reddy et al (144) did not even report study values for the most part, and they only described an evaluation of the VAS.

These studies are therefore listed in Table 1 in parentheses. They were still included in the meta-analysis, however, because they contained data on other outcome parameters considered in the current meta-analysis.

It was possible to generate a control group called "conservative therapy" (including epidural steroid injection) from the control groups of the 27 studies in Table 1 that were included for this meta-analysis.

We decided to assign patients treated with epidural steroid injection to the control group "conservative therapy" because other studies proceeded likewise (152,153).

Here too, however, the studies by Nardi et al (143) and Birnbaum (28) could not be taken into consideration due to missing study data or standard deviations, as was the case for the analysis of VAS data on nucleoplasty.

Complication Rate

The complication rate calculated here includes all events assessed in the studies as complications. Most of the studies reported no or no significant complications. If no information on complications was found, the study had to be excluded from the calculation of the meta-analysis.

However, if it was reported that no complications had occurred and clinically relevant problems after nucleoplasty were still described, these values were then adjusted correspondingly based on the description for this meta-analysis. This had to be followed for the papers by Bhagia et al from 2006 (132) and Sinan et al from 2011 (148) described below.

ODI

The ODI values for the nucleoplasty group in the study by Bokov et al (117) had to be calculated as the ones for VAS/NPS. Based on the respective group size and the study values, it was possible to calculate a new total value from 3 differently sized subgroups treated with nucleoplasty for disc herniations of different severities.

The study by Shabat et al (145) reported neither exact ODI values nor standard errors; therefore, we did not take this article into account in the meta-analysis.

Results

The remaining 27 articles consisted of 22 prospective and 5 retrospective studies. Among these 27 clinical studies, 4 were randomized, controlled studies and 3 others were controlled, non-randomized studies. The remaining 20 studies were non-interventional studies (NIS). Altogether, 3,211 patients were treated with nucleoplasty in the 27 studies.

VAS

In the 17 studies using VAS/NPS as outcome parameters, 971 patients underwent nucleoplasty. Four of these studies had control groups comprising 230 patients total. Nucleoplasty affected a significant drop

Table 4. *Pain reduction after nucleoplasty total (cervical + lumbar).*

Random effects analysis	Patients	VAS / NPS nucleoplasty total	95% CI	P values in comparison to baseline
Baseline	971	7.27	[7.03; 7.51]	
1 day	125	2.12	[1.65; 2.59]	< 0.001
1 week	42	2.50	[2.42; 2.58]	< 0.001
2 weeks	275	2.70	[1.72; 3.68]	< 0.001
1 month	589	3.23	[2.57; 3.89]	< 0.001
6 weeks	102	2.66	[2.59; 2.73]	< 0.001
3 months	612	2.84	[2.45; 3.23]	< 0.001
6 months	790	3.06	[2.60; 3.53]	< 0.001
12 months	702	3.03	[2.15; 3.92]	< 0.001
18 months	73	1.54	[1.16; 1.91]	< 0.001
24 months	92	3.69	[3.34; 4.04]	< 0.001

Table 5. *Pain reduction after conservative therapy (including epidural steroid injection).*

Random effects analysis	Patients	VAS / NPS conservative therapy	95% CI	*P* values in comparison to nucleoplasty total
Baseline	98	6.98	[5.91; 8.04]	0.599
6 weeks	91	5.76	[5.20; 6.33]	*< 0.001
3 months	88	4.87	[3.86; 5.89]	*< 0.001
6 months	85	4.25	[2.61; 5.90]	0.173
12 months	57	3.85	[3.77; 3.92]	0.073

* Significant improvement of nucleoplasty in comparison to conservative therapy ($P < 0.05$)

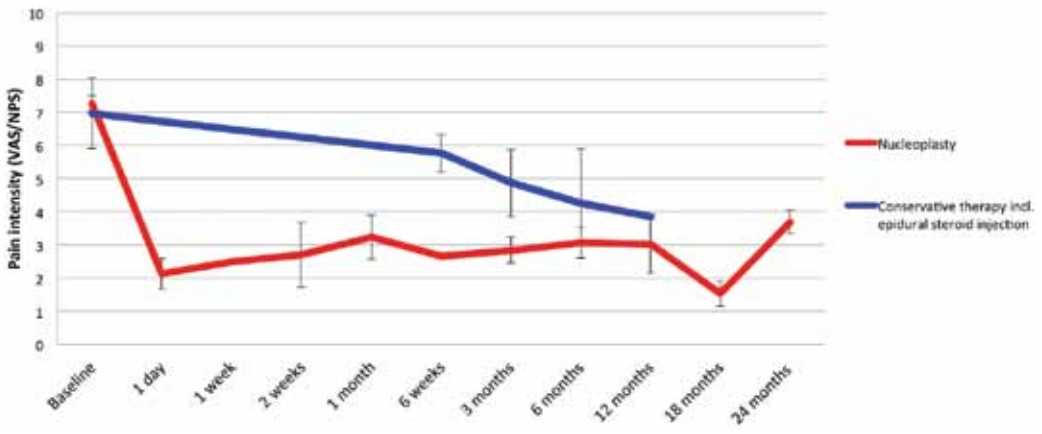

Fig. 2. *VAS/NPS values after nucleoplasty total and conservative therapy.*

in pain intensity compared to baseline at every measurement time point (Table 4).

In contrast, conservative therapy did not show a significant difference compared to baseline until after one year. Nucleoplasty was significantly superior to conservative therapy after 6 weeks and after 3 months (Table 5).

Fig. 2 shows the nucleoplasty VAS/NPS values calculated in the meta-analysis compared to conservative therapy (including epidural steroid injection), depicted at each of the measurement time points in the included studies.

The calculated VAS/NPS values for cervical nucleoplasty as well as those for lumbar nucleoplasty are presented in Fig. 3, likewise depicted at the measurement time points in the included studies. In all, 761 patients with lumbar and 210 patients with cervical disc herniations were treated. Cervical nucleoplasty appeared to bring greater pain relief compared to lumbar nucleoplasty; the difference, however, was not significant at any time point.

The values for the subgroup analysis for microdiscectomy and Dekompressor were not depicted because comparative individual studies have illustrated them sufficiently (29,117,139). These values, however, were taken into consideration when calculating the nucleoplasty VAS/NPS values.

Complication Rate

Twenty-five studies comprising 3,069 patients in the nucleoplasty group were available for calculating the complication rate. Five studies had a control group with 168 patients total. The complication rate was 1.5% for nucleoplasty and 4.0% for the entire group of control procedures (Figs. 4 and 5). The most frequent complications were postoperative discitis and tingling/numbness or leg pain.

Since this value for nucleoplasty involves a pooled value from a meta-analysis, the true value for nucleoplasty lies between 0.7% and 3.0%, thus definitely in

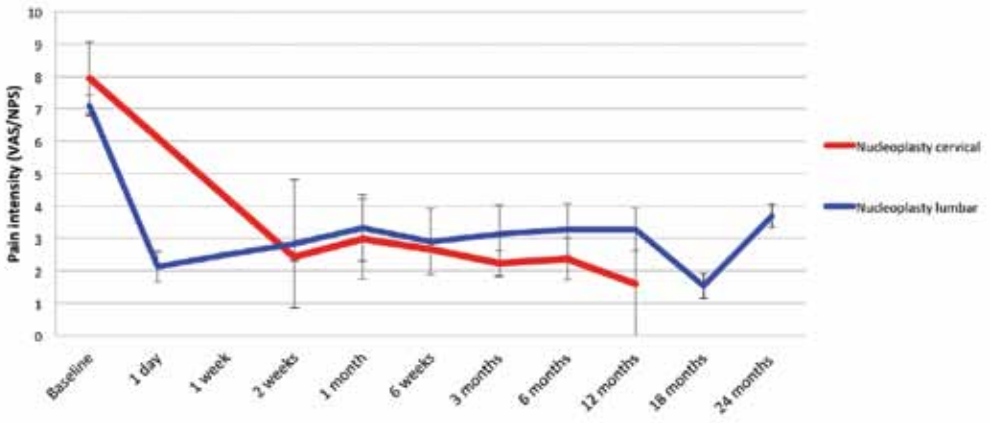

Fig. 3. *VAS/NPS values after nucleoplasty for herniated cervical and lumbar discs.*

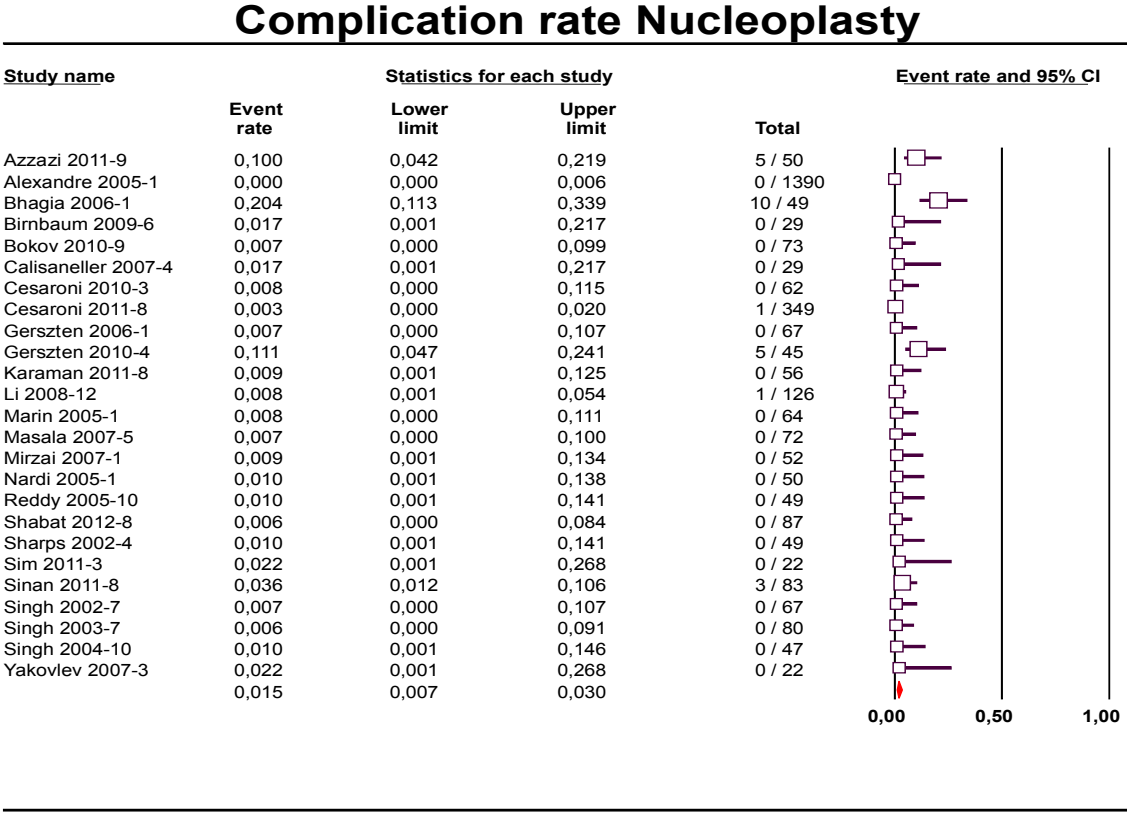

Fig. 4. *Meta-analysis complication rate – nucleoplasty.*

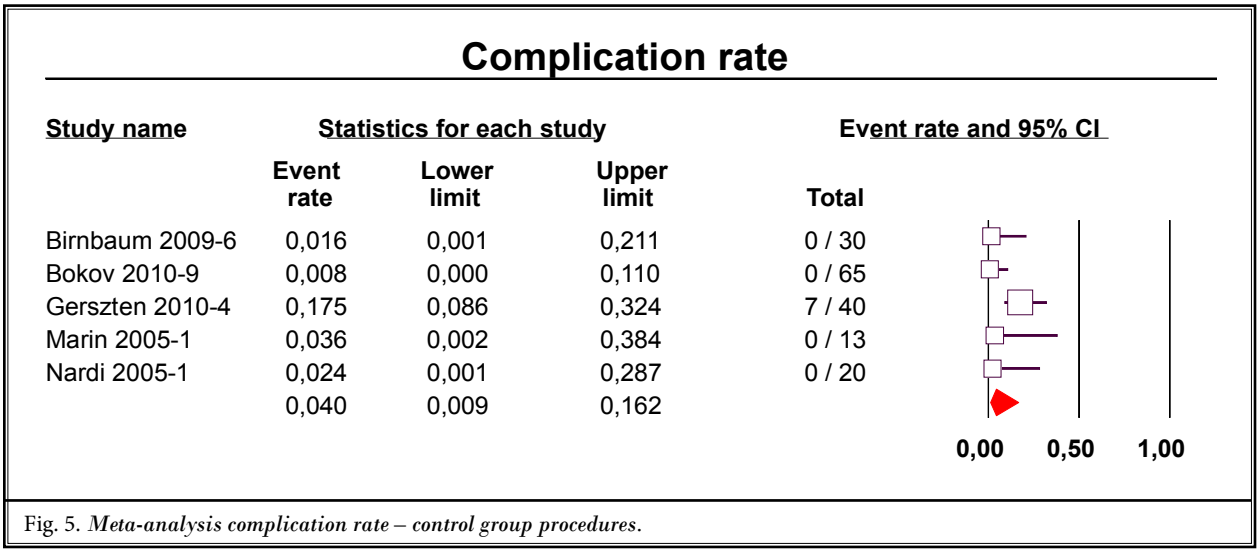

Fig. 5. *Meta-analysis complication rate – control group procedures.*

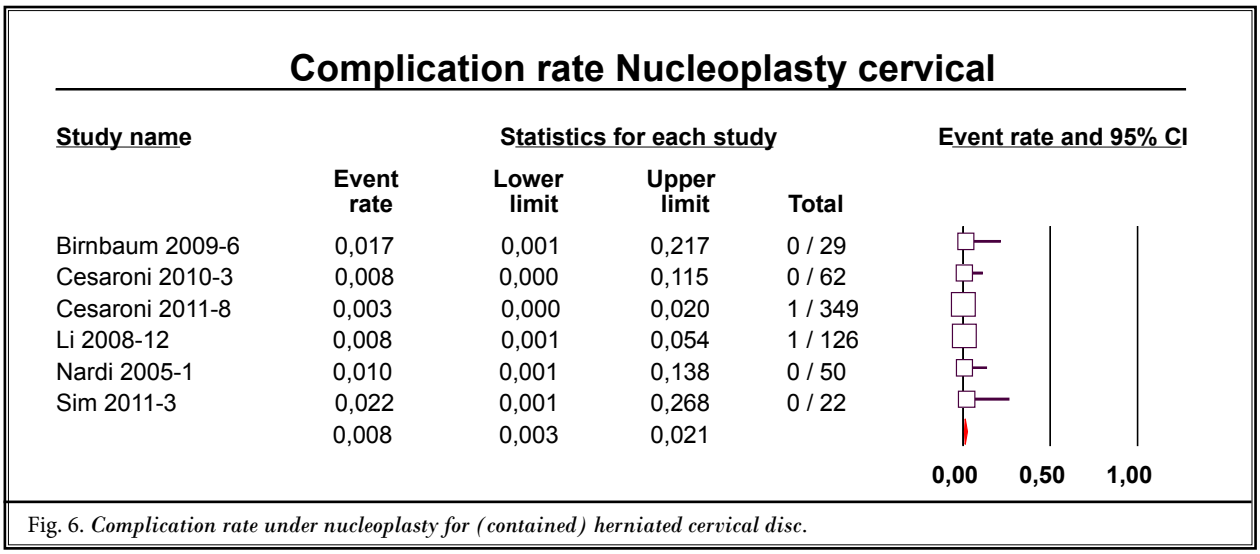

Fig. 6. *Complication rate under nucleoplasty for (contained) herniated cervical disc.*

a low range. This stands in contrast to the value for control procedures between 0.9% and 16.2%, which represents an extreme span reaching into the unacceptable. The complication rate under nucleoplasty for herniated cervical discs was 0.8% (n = 638 patients) and for herniated lumbar discs 1.8% (n = 2,237 patients) (Figs. 6 and 7).

ODI

Six studies, 2 of which had control groups, were available for the calculation of ODI values. The nucleoplasty group had a sample size of 318 patients and the control group had 105 patients. All patients underwent lumbar nucleoplasty.

Nucleoplasty showed a significant drop at all time points compared to baseline (58.95), thus revealing improvement in the patients' functional mobility (Table 6).

Fig. 8 shows the ODI values for nucleoplasty as calculated in the meta-analysis in comparison to those for epidural steroid injection, depicted at the measurement time points in the included studies. Nucleoplasty therefore shows a significant decrease and thus improvement in the ODI compared to baseline across all time points. After 3 months and after 6 months, a significantly better ODI can be seen for nucleoplasty than for conservative therapy. All other measured values are also lower, although not significantly.

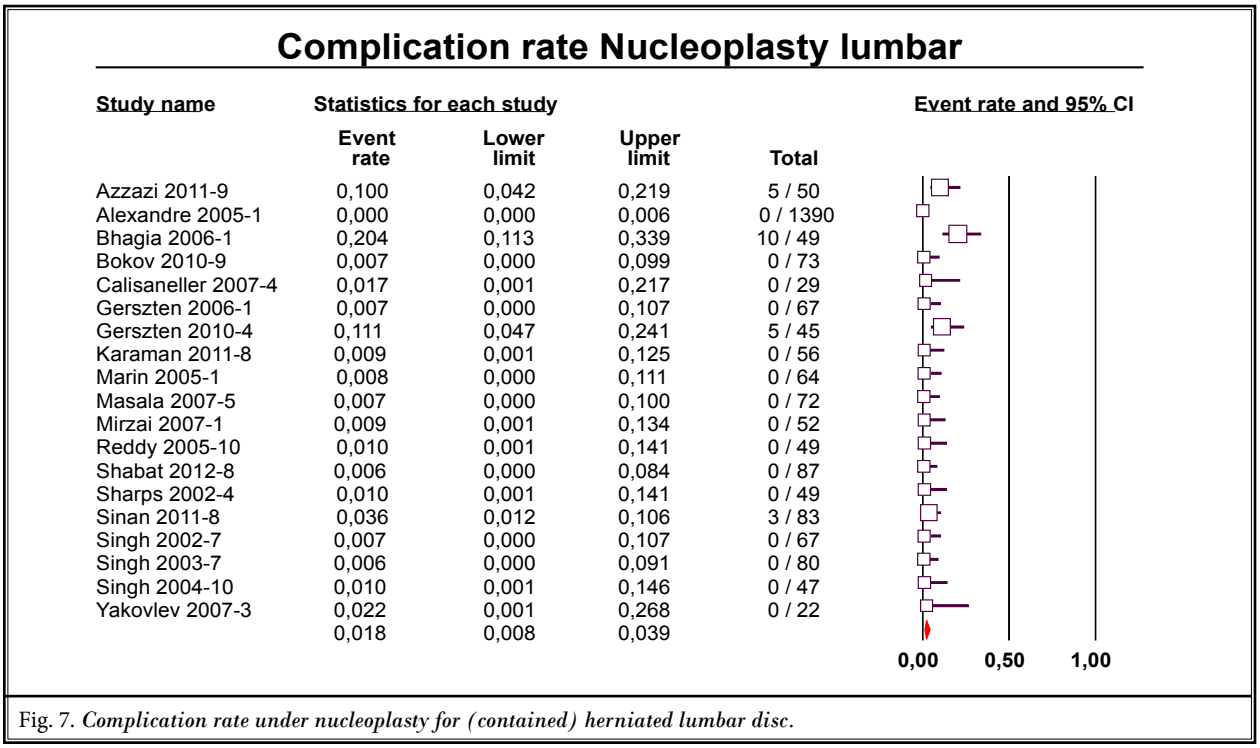

Fig. 7. *Complication rate under nucleoplasty for (contained) herniated lumbar disc.*

Table 6. *Functional mobility after nucleoplasty and after conservative therapy (including epidural steroid injection).*

Random effects analysis	Patients	ODI nucleoplasty	95% CI	*P* values in comparison to baseline
Baseline	318	58.95	[45.47; 72.43]	
1 week	42	28.60	[26.12; 31.08]	< 0.001
2 weeks	50	29.00	[26.26; 31.74]	< 0.001
1 month	179	23.21	[9.33; 37.09]	< 0.001
6 weeks	40	30.00	[24.42; 35.58]	< 0.001
3 months	153	18.30	[8.40; 28.19]	< 0.001
6 months	256	22.54	[10.94; 34.13]	< 0.001
12 months	264	24.43	[13.08; 35.79]	< 0.001
18 months	73	12.82	[9.16; 16.47]	< 0.001
24 months	92	36.98	[31.63; 42.33]	< 0.005
	Patients	**ODI conservative therapy (including epidural steroid injection)**	**95% CI**	***P* values in comparison to nucleoplasty**
Baseline	40	43	[37.73; 48.27]	*< 0.05
6 weeks	33	38	[33.22; 42.78]	*< 0.05
3 months	30	40	[33.92; 46.08]	*< 0.001
6 months	28	49	[43.44; 54.56]	*< 0.001

* Significant improvement of nucleoplasty in comparison to conservative therapy ($P < 0.05$)

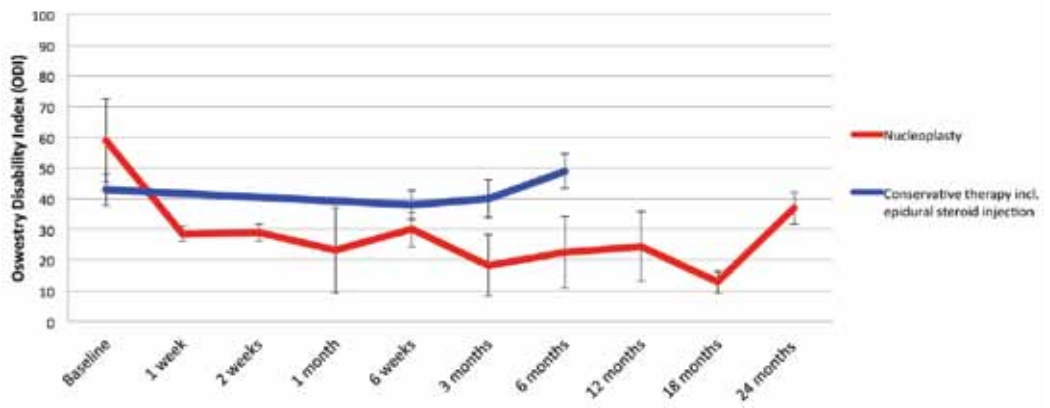

Fig. 8. *ODI values after nucleoplasty (lumbar) and conservative therapy.*

Discussion

In the recent past, several reviews on nucleoplasty have appeared; a meta-analysis, however, has not yet been carried out (17,22,23). The review and corresponding meta-analysis presented here provides pooled data on VAS and ODI values as well as an overall complication rate for the selected clinical studies. It was possible to summarize the treatment success of nucleoplasty in previous clinical studies based on the chosen outcome parameters, although we were not able to make a recommendation or evaluation, let alone a catalog of indications. The results, therefore, are conclusions about the effectiveness and safety of the nucleoplasty procedure, as are the intention of a meta-analysis (154).

The studies used in this meta-analysis are heterogeneous for the most part, which is reflected in the varying scores of the studies on the Jadad scale. In order to obtain homogeneity, we applied the Jadad scale to each study and set the minimal score at 2. This may appear low at first glance, but it can be noted that the included studies contained a specific intervention for a specific indication, namely nucleoplasty for intervertebral disc conditions, with defined measurement time points and intervals suitable for the calculation of a meta-analysis, thus fulfilling the inclusion criteria for this meta-analysis (155).

Particularly for the outcome parameter "complication rate," studies with a low Jadad scale score were also included that were not considered in the analysis of VAS and ODI. Nonetheless, precisely these studies treated patients – successfully – using nucleoplasty, and for that very reason the studies with low Jadad scores were also considered in this meta-analysis. Moreover, one must question whether blinding and randomization in an interventional study on nucleoplasty is necessary at all in order to obtain valid data, since nucleoplasty was also applied successfully even without blinding and randomization.

Setting a low Jadad scale score may reduce the quality of the meta-analysis, yet the meta-analysis should be as meaningful and reliable as possible for the given clinical aspect.

Furthermore, the meta-analysis calculation drew upon a "random effects" model, which takes possible heterogeneity into consideration more than the "fixed effect" model, since the confidence intervals are spread more broadly and thus capture the true value of the meta-analysis. This is therefore a more cautious and conservative estimation, but it can also result in greater inaccuracy through the overestimation of smaller studies and constitute a higher risk for the bias of the (nucleoplasty) results (156).

A (selection) bias could have resulted by excluding the studies by Li et al (108), Fabrizi et al (109), and Theron et al (110). However, the indication for nucleoplasty and the use of Coblation technology, respectively, did not fulfill the corresponding inclusion criterion of the present meta-analysis, namely the clinical application of nucleoplasty for intervertebral disc conditions.

As shown in Table 2, the inclusion and exclusion criteria of the studies were relatively consistent. However, Karaman et al (138) and Mirzai et al (142), for example, excluded patients over 60 years of age from their studies, maintaining that the aging intervertebral disc increasingly dehydrates and undergoes fibrotic changes.

Interestingly, the study by Sim et al (147) treated 5 patients with nucleoplasty even though contraindications existed according to their exclusion criteria; 2 patients had disc extrusions and 3 patients had spinal stenosis. However, one patient with disc extrusion showed excellent and the other had good results. Of the 3 patients with spinal stenosis, one showed excellent and the other 2 had fair results.

Bokov et al (117) treated 27 patients with disc extrusions. Although the authors concluded that nucleoplasty in these patients was associated with a poor outcome, stable and significant pain relief was observed in 44% of the patients and even total pain relief in 15% of the patients. This was another reason to also include patients with disc extrusions in the present meta-analysis.

In the study by Gerszten et al (136), an inclusion criterion for nucleoplasty and for the control group receiving epidural steroid injection was that the patients had already undergone failed epidural steroid injection 3 weeks to 6 months prior to study onset. This could have led to bias of the measurement results especially in the nucleoplasty group, as the patient's psyche may constitute a significant factor in coping with the disease.

In their studies, Singh et al (18-20) excluded all patients who used opioids heavily. Since patients with chronic back pain frequently consume strong opioids for prolonged periods of time, this selection of patients could have led to bias.

Consequently, it cannot be ruled out with certainty that the inclusion and exclusion criteria defined in the included studies caused a possible bias with regard to the patient population and the calculated values for the outcome parameters. Since patients with higher grade spinal degenerations and disc extrusions were included in the studies and consecutive in this meta-analysis, the resulting calculations are likely to be somewhat negatively biased.

VAS

The application of nucleoplasty results in significant pain reduction at every examination time point compared to baseline, and the patients experienced measurable and, above all, noticeable pain relief.

The need for calculating total VAS values for various areas of pain (e.g., back and leg pain) in patients from the studies by Bhagia et al (132), Gerszten et al (136), Lemcke et al (139), and Zhu et al (150) may have caused biased results. Also, the assumption of a correlation for the study by Bhagia et al (132) and the assumption of a standard deviation for the study by Singh et al (19) from their earlier study (18) may also constitute sources of interference, yet they are based on the procedural instructions for meta-analyses as recommended by the Cochrane Collaboration (151).

Karaman et al (138) found that age had no significant effect on VAS values, but a remarkable, negative correlation existed with the duration of pain symptoms.

Lemcke et al (139) observed in their comparative study nucleoplasty vs. "Disc Dekompressor" significantly lower VAS values in the Disc Dekompressor group. The authors attributed this result to lacking randomization and the clearly different symptom durations (nucleoplasty 30.5 months vs. Disc Dekompressor 16 months). Interestingly, in the nucleoplasty group a weak correlation was noted between patient age and outcome, so that younger patients exhibited better results than older patients.

In the study by Bokov et al (117), 3 subgroups were treated with nucleoplasty. Based on the size of the disc protrusion, patients were divided into subgroup 1a or 1b. Patients with extrusions were assigned to group 2. In the calculation carried out here, these 3 groups were added together to form one treatment group with pooled VAS data. Since patients with extrusions are actually a contraindication for nucleoplasty, subgroup 2 could have had a negative bias on the total VAS value.

The third patient group was treated using microdiscectomy. Bokov et al (117) concluded from their study results that the size of the disc protrusion does not constitute a predictor of success; in cases of extrusions, however, nucleoplasty yields unsatisfactory results significantly more often compared to microdiscectomy.

In the studies conducted by Singh et al (18-20) from 2002 to 2004, NPS values were documented instead of VAS values, which still lead functionally to analog test results.

Reddy et al (144), Bhagia et al (132), Yakovlev et al (149), Bokov et al (117), and Zhu et al (150) administered a dose of glucocorticoid (mostly betamethasone) and a local anesthetic (mostly lidocaine) immediately after nucleoplasty (in part only to patients with radicular symptoms). This could certainly have had a positive influence on the VAS/NPS as well as the ODI values in the short and medium term.

Complication Rate

The complication rate for nucleoplasty was 1.5% (0.8% for cervical, 1.8% for lumbar nucleoplasty). In no case of nucleoplasty were reports made of severe

complications such as paraplegia or even death. The low complication rate may most likely be explained by the minimally invasive, percutaneous procedure of nucleoplasty. The unequal complication rates for cervical and lumbar nucleoplasty are most likely due to the different sides of needle entry. An anterior access site is chosen for cervical nucleoplasty, meaning that nerve structures are not passed, and less soft tissue simplifies the depiction of the intervertebral regions.

The complication rate calculated in this meta-analysis includes all events evaluated as complications in the studies. Most studies reported no or no significant complications. If no information pertaining to complications was found, the study had to be deleted from the meta-analysis calculation. It may be assumed, however, that no complications occurred at all, since clinical studies are required to publish any and all occurring complications. Thus, the real complication rate may lie below the rate calculated in this meta-analysis. The following studies demonstrate that the definition of complications was not uniform:

As described previously, the complication rate was adapted for the articles by Bhagia et al (132) and Sinan et al (148).

Bhagia et al (132) conducted a study on side effects and complications that occurred after nucleoplasty. The most important side effects were pain at the puncture site (76% of patients) and newly appearing back pain (26%). At the end of the study after 2 weeks, patients no longer complained about these 2 symptoms. At the middle of the observation period after one week, 14 out of 53 patients noticed newly occurring numbness in the legs which, however, only 10 patients indicated having at the end of the study after 2 weeks. In no case did the numbness cause functional restrictions, and dermatomal mapping of such numbness was not possible, suggesting that the numbness did not involve the compression of a nerve root. Nevertheless, the sensation of numbness was assessed as a complication since the further course was unclear. Due to the short observation period, the later condition of the patients is described insufficiently. Even if the complication rate for this study may possibly seem to be too high in the present meta-analysis, it still appears justifiable to take it into consideration.

Sinan et al (148) stated in their abstract that no complications had been observed. In the results section, however, they reported of 2 patients who had experienced numbness in both legs for 3 months; another patient developed discitis that was able to be treated successfully with spondylodesis. It therefore appears that the authors restricted the description "complications" to hemorrhage, meningitis, and nerve damage. These 3 complications were taken into consideration for the present meta-analysis, since other authors had also described discitis (127,131,135) and numbness as complications (132).

The study by Gerszten et al (136), which compared nucleoplasty with epidural steroid injection, is the only study that describes the complication rate in percent, calls complications "procedure-related adverse events," and defines them very broadly. The complication rate was 11% in the nucleoplasty group (5 patients with 7 events) and 18% in the epidural steroid group (7 patients with 14 events). Pain at the puncture site, for example, was evaluated here as an event. This event could be considered self-limiting (2 events each per examined group). However, the authors also documented increased radicular pain (1 vs. 5 events), increased numbness (1 vs. 0 events), increased back pain (1 vs. 4 events), light-headedness (0 vs. 1 event), and muscle tightness (0 vs. 1 event). Whether these events were self-limiting and how the authors then proceeded with the patients is not mentioned. Since the affected patients were able to report more than one complication, the complication rate could not be lowered in the present meta-analysis.

ODI

Nucleoplasty shows a significant decrease at all measurement time points compared to baseline and thus an improvement in patients' functional mobility.

Despite the efficacy of epidural steroid injection in cervical (157) and lumbar (158) disc herniations and the cost effectiveness (159) as demonstrated in other studies, at no time did our meta-analysis show significant improvement in control group patients who were treated with conservative therapy including epidural steroid injection. This could be explained by the purely short-term effect of a drug such as glucocorticoids and/or local anesthetics.

As described above, Reddy et al (144), Bhagia et al (132), Yakovlev et al (149), Bokov et al (117), and Zhu et al (150) administered a dose of glucocorticoid (mostly betamethasone) and local anesthetic (mostly lidocaine) immediately following nucleoplasty. Here, too, the ODI values could surely have been influenced positively in the short and the medium term.

For the same indication reasons stated above, we decided to compare nucleoplasty with conservative therapy.

The different ODI baseline values in the nucleoplasty group (ODI of 59) compared to the conservative control group (including epidural steroid injection) (ODI of 43) as shown in the subgroup analysis cannot be explained by the inclusion of nonrandomized studies. It seems conceivable that patients with more severe symptoms may be more likely to receive a doctor's recommendation for nucleoplasty.

Conclusions

Nucleoplasty reduces pain in the long term and increases patients' functional mobility. Compared to other treatments, it is an effective, low-complication, minimally invasive procedure used to treat cervical and lumbar disc herniations. Under the given catalog of indications, it appears to be superior to conservative therapy. Patients experience greater pain relief after cervical nucleoplasty than after lumbar nucleoplasty.

Studies published to date show a heterogeneous picture of inclusion and exclusion criteria. Therefore, a bias of the data presented here cannot be ruled out with certainty. Initial results suggest the possibility of extending the indication to include disc extrusions.

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