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Systematic Review

A Systematic Review on the Effectiveness of the Nucleoplasty™ Procedure for Discogenic Pain

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Background: Nucleoplasty is a minimally invasive procedure for treating pain caused by symptomatic disc herniation that is refractory to conservative therapy. Observational studies have reported differing outcomes for this procedure and thus its effectiveness is yet to be determined.

Study design: A systematic review of the efficacy of the nucleoplasty procedure.

Objectives: To assess the clinical efficacy of the nucleoplasty procedure for treating back pain from symptomatic, contained disc herniation and to evaluate the methodological quality of the included studies.

Methods: The relevant literature for nucleoplasty was identified through a search of the following databases: Pubmed, Ovid Medline, and the Cochrane library, and by a review of the bibliographies of the included studies. A review of the literature of the effectiveness of the nucleoplasty procedure for managing discogenic pain was performed according to the criteria for observational studies using a "Quality Index" scale to determine the methodological quality of the literature. The level of evidence was classified as Level I, II, or III based on the quality of evidence developed by the United States Preventive Services Task Force (USPSTF) for therapeutic interventions. Recommendations were based on the criteria developed by Guyatt et al.

Outcome measures: The main outcome measures evaluated were the percentage of pain relief based on visual analogue scale (VAS) or numeric rating scale (NRS), percentage of patients with more than 50% reduction in pain, percentage of patients meeting one or more success criteria after nucleoplasty, and improvement in patient function. Secondary measures noted were reports of complications and the Quality Index scores of each study that was evaluated.

Results: The quality of evidence for improvement in pain or function after a nucleoplasty procedure is Level II-3. The recommendation is 1C/strong for the nucleoplasty procedure based on the quality of evidence available. The median Quality Index score was 16 (range 12 – 19), indicating adequate methodological quality of the available literature. None of the studies reported major complications related to nucleoplasty.

Conclusions: Observational studies suggest that nucleoplasty is a potentially effective minimally invasive treatment for patients with symptomatic disc herniations who are refractory to conservative therapy. The recommendation is a level 1C, strongly supporting the therapeutic efficacy of this procedure. However, prospective randomized controlled trials with higher quality of evidence are necessary to confirm efficacy and risks, and to determine ideal patient selection for this procedure.

Key words: Nucleoplasty outcomes, contained disc herniation, percutaneous disc decompression, Quality Index, discogenic pain, systematic review

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The majority of patients with discogenic back pain improve without requiring intervention. Open spine surgery may be considered for cases of symptomatic disc herniation producing persistent back and leg pain that is intractable to conservative therapy. However, spine surgery may be followed by significant morbidity including the development of postoperative epidural fibrosis and scar formation, disc reherniation, injury to the nerve root, trauma to the cauda equina, vascular complications, the development of "failed back surgery" syndrome, and discitis (1,2). Furthermore, patients with small, contained degenerated discs are not ideal surgical candidates, as discectomy often does not result in significant relief of symptoms in this population (3,4). Therefore, minimally invasive percutaneous disc procedures may be preferable to open surgery in certain clinical situations.

Percutaneous disc decompression (PDD) describes a number of minimally invasive disc procedures that aim to relieve pressure on sensory structures while minimizing trauma to normal tissues and enhancing patient recovery (5-9). Historically, these techniques have included chymopapain chemonucleolysis, which produces an enzymatic break of the nucleus (10), vaporization with laser (7,11,12), and mechanical tissue resection with manual or automatic nucleotomy (6,13,14) or with endoscopic techniques (15). Also, patients with internal disc disruption (IDD), which is a distinct clinical entity from a herniated or protruding disc, have been treated with intradiscal electrothermal nucleoplasty (IDET) (11,16). However, despite reports of clinical success in properly selected patients, there have been drawbacks attributed to each technique. For example, chemonucleolysis with chymopapain has been known to cause severe anaphylactic reactions in some patients (10). Nucleotomy procedures can cause nerve root injury and cauda equina syndrome (17,18). Both laser discectomy and IDET can cause postoperative pain and back spasm, which can confound outcome assessment and post-procedure rehabilitation (11,12,16). Recently, for contained disc herniations, 2 new procedures have been introduced: Disc Nucleoplasty™ and the Dekompressor™" techniques.

In July of 2000, Disc Nucleoplasty™, a method of percutaneous disc decompression using coblation technology, was approved by the US Food and Drug Administration (FDA). The procedure involves removing a portion of the nucleus tissue using a one mm diameter bipolar instrument that creates radiofrequency energy that excites the electrolytes in the disc. The energized particles have a sufficient force to break down molecular bonds, which dissolves the soft tissue material of the disc nucleus. Removal of tissue at relatively low temperatures (typically 40°C to 70°C) preserves the integrity of surrounding healthy tissue, therefore reducing the risk of damage to remaining disc tissue and the end-plate cartilage (19). In an intact disc, this small volumetric reduction of the nucleus pulposus results in a disproportionate decrease in pressure, thereby relieving some of the chemical and mechanical factors causing pain (20). Approximately 1 mL of disc tissue volume is removed, corresponding to a reduction of the discal volume by about 10 to 20%. Reduced intradiscal pressure following this procedure has been confirmed in studies on cadaveric specimens, although it has been found that degenerated discs have less pressure reduction than normal discs (21). Studies have also found that neovascularization of tissues can occur following this procedure, suggesting that regeneration and healing of the disc may result, which may be another mechanism for pain improvement.

A number of observational studies of variable methodological quality have reported on patient outcomes following the nucleoplasty procedure for contained herniated discs. Many of these studies were non-randomized single site reports that needed further confirmation of their results or were side-to-side comparisons between similar studies. A recent systematic review (9) showed limited evidence.

Thus, the objective of this systematic review is to assess the efficacy of the nucleoplasty procedure for therapy of symptomatic, contained disc herniations with regard to pain relief and functional status, to evaluate the reported incidence and nature of complications associated with this procedure, and to critically review the methodological quality of the available literature.

Methods

Literature Search

The terms "nucleoplasty," "percutaneous disc decompression," and "coblation" were identified in the published English-language literature by searching several electronic databases, including PubMed (1966 – September 2008), Ovid Medline (1968 – September 2008), and the Cochrane library (1980- September 2008). The authors also reviewed the bibliographies of studies identified by the electronic database search in order to potentially locate additional trials for the review. We

identified 14 trials studying a total of 717 subjects that met the inclusion criteria for the present review. The search was conducted independently by 2 authors (FJG and SSN) and then compared for reliability. Data from each study were independently extracted by both authors and compared using data extraction forms.

Selection Criteria

Specific inclusion and exclusion criteria were used in considering which articles were appropriate for this systematic review. Included in our analysis were studies of adult patients, both genders, with chronic back, neck, and/or extremity pain who were treated with the nucleoplasty procedure. Furthermore, inclusion criteria reflected pain that was caused by a contained herniated disc that was refractory to conservative therapy. Only articles that used standardized measures of pain and/or function were included. Excluded from our analysis were case reports, narrative reviews, animal studies, cadaveric or biomechanical studies, and articles reporting non-clinical outcomes. Our literature analysis was limited to only peer-reviewed published works. Although numerous reports on nucleoplasty have been presented at scientific meetings, these were also excluded.

Method of Review

Outcome Parameters

Primary outcome measures that were evaluated included validated pain scales such as the visual analogue scale (VAS), percentage of patients with more than 50% pain relief, 2-point reduction in pain severity, percentage of pain relief, and functional improvement in sitting, standing, and walking. Using data extraction forms, data from each study concerning complications from nucleoplasty was reviewed by both authors.

Methodologic Quality Assessment

One of the limitations in reviewing the available literature is that most studies on nucleoplasty are observational and non-randomized. We used a standardized instrument called the Quality Index to assess the methodological quality of the included studies (Table 1) (22). The Quality Index is a 27-item, partially validated checklist that assesses the reporting quality, external and internal validity, bias, confounding factors, and power of non-randomized and randomized studies. The Quality Index method is useful to compare observational and other non-randomized studies, and scores may range from 0 to 32. For observational studies, a quality score of 12 or greater is considered excellent (23). For overall methodological assessment of study quality, 2 authors of this analysis (FJG and SSN) independently calculated Quality Index scores for each study and consensus was achieved for any disagreements. The median values and range for each category of the Quality Index scale were also calculated. Studies with a quality index score of less than 12 were excluded from our analysis (24).

The methodological quality assessment tool used in this review differs from the methodological quality assessment criteria utilized for other systematic reviews published in this journal (6-9,25-31). The application of different criteria will provide validity to the process rather than repeating the same criteria.

Both quantitative and qualitative data synthesis were performed for the purposes of this review. Numerical data on pain scores, percentage of pain relief, and functional improvement were extracted from each study and similar outcome measures were grouped wherever possible. When possible, studies examining the same outcome variables were grouped together, a subgroup analysis was conducted, and the median values and range of each outcome variable were calculated. The complications reported in each of the studies were noted, with the reporting of complications being primarily qualitative.

A meta-analysis was performed for pain scores, which was the primary outcome variable denoted in the majority of the studies. The purpose of the meta-analysis was to derive a "pooled" or combined estimate of the VAS at the various time points: baseline, one month, 3 months, 6 months, and 12 months after procedure. The pooled estimate at each time point was calculated using a weighted average of the estimates from the individual studies via accepted meta-analysis techniques (32). The "weights" used in the meta-analysis take into account the sample size from each individual study. Both fixed and random effect models were used, but there was significant heterogeneity among the studies using the test statistic proposed by DerSimonian and Laird (33), so we needed to use a random effects model to calculate a pooled estimate. The mean VAS scores over time are correlated since they involve repeated measures on the same patients. Unfortunately, we did not have access to the correlations from all of the studies in the review. However, treating the mean scores as independent gives a conservative *P*-value compared to methodology that takes the correlation into account (34). Thus, differences between means over time may be even stronger

Table 1. *Modified Quality Index assessment criteria for methodology of studies*

Criterion	Weighted Score (points)
Reporting	**11**
• Is the hypothesis/aim/objective of the study clearly described?	1
• Are the main outcomes described in the Introduction or Methods?	1
• Are the characteristics of the patients clearly described?	1
• Are the interventions of interest clearly described?	1
• Are the distributions of principal confounders clearly described?	2
• Are the main findings of the study clearly described?	1
• Does the study provide estimates of random variability for outcomes?	1
• Have all important adverse events been reported?	1
• Have the characteristics of patients lost to follow-up been described?	1
• Have actual probability values been reported for main outcomes?	1
External Validity	**3**
• Were subjects who were asked to participate representative of the entire population?	1
• Were those subjects who were prepared to participate representative of the entire population?	1
• Were the staff and facilities where the patients were treated representative of the treatment the majority of patients receive?	1
Internal Validity - Bias	**7**
• Was an attempt made to blind study subjects to the intervention they have received?	1
• Was an attempt made to blind those measuring the main outcomes?	1
• If the results were based on "data dredging," was this made clear?	1
• Is the time period between interventions and outcomes the same for cases and controls?	1
• Were statistical tests used to assess the main outcomes appropriate?	1
• Was compliance with the intervention/s reliable?	1
• Were the main outcome measures used accurate (valid/reliable)?	1
Internal Validity – Confounding (selection bias)	**6**
• Were the groups, cases, and controls recruited from the same population?	1
• Were study subjects in different groups recruited over the same period of time?	1
• Were study subjects randomized to intervention groups?	1
• Was the randomized assignment concealed from both patients and health care staff until recruitment was complete?	1
• Was there adequate adjustment for confounding?	1
• Were losses of patients to follow-up taken into account?	1
Power	**5**
• Did the study have sufficient power to detect a clinically important event where the probability due to chance is less than 5%?	5
TOTAL SCORE	**32**

Adapted and modified from Downs et al. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377-84 (22).

Table 2. *Quality of evidence developed by USPSTF*

I:	Evidence obtained from at least one properly randomized controlled trial
II-1:	Evidence obtained from well-designed controlled trials without randomization
II-2:	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II-3:	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III:	Opinions of respected authorities, based on clinical experience, descriptive studies, and case reports or reports of expert committees

Adapted from the U.S. Preventive Services Task Force (USPSTF) (35).

Table 3: *Grading Recommendations*

Grade of Recommendation/ Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2B/weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	RCTs without important limitations or overwhelming evidence from observational studies	Very weak recommendations; other alternatives may be equally reasonable

Adapted from Guyatt G et al. Grading strength of recommendations and quality of evidence in clinical guidelines. Report from an American College of Chest Physicians Task Force. *Chest* 2006;129:174-81 (36).

than what our results suggest.

Analysis of Evidence

Qualitative analysis of the studies that were selected for this review was conducted using 5 levels of evidence, ranging from Level I to III with 3 subcategories in Level II, as illustrated in Table 2 (35). This analysis was conducted using the guidelines set forth by the U.S. Preventive Services Task Force (USPSTF) (36).

Grading

Grading recommendations were based on Guyatt et al's criteria as illustrated in Table 3 (36).

Outcome of the Studies

A study was judged to be positive if the nucleoplasty treatment was effective, with outcomes reported at the reference point with positive or negative results at one month, 3 months, 6 months, and one year. Note that all but one of the studies evaluated in our review were observational in design.

In evaluating the literature on nucleoplasty, a ma-

jor problem in assessing the results and comparing outcomes was in the heterogeneity between the subjects included in each trial and in the way outcomes were reported. Both clinical heterogeneity (as indicated by significant variability on the way outcomes were studied between each trial) as well methodological heterogeneity (as indicated by variability in study design and quality) were present. As all of the studies were observational in nature and often based on differing inclusion criteria, only limited subgroup analysis could be conducted for reporting outcomes. In our results section, we report on the potential causes of heterogeneity between different trials, with consideration to the factors that may have led to outlying results from those found in the majority of studies.

Results

The literature search, completed in September 2008, yielded 62 abstracts and full articles that were at least potentially relevant studies for this review. Further independent review of these references yielded 40 peer-reviewed articles that apparently met the inclusion criteria. A final review yielded a total of 14 trials

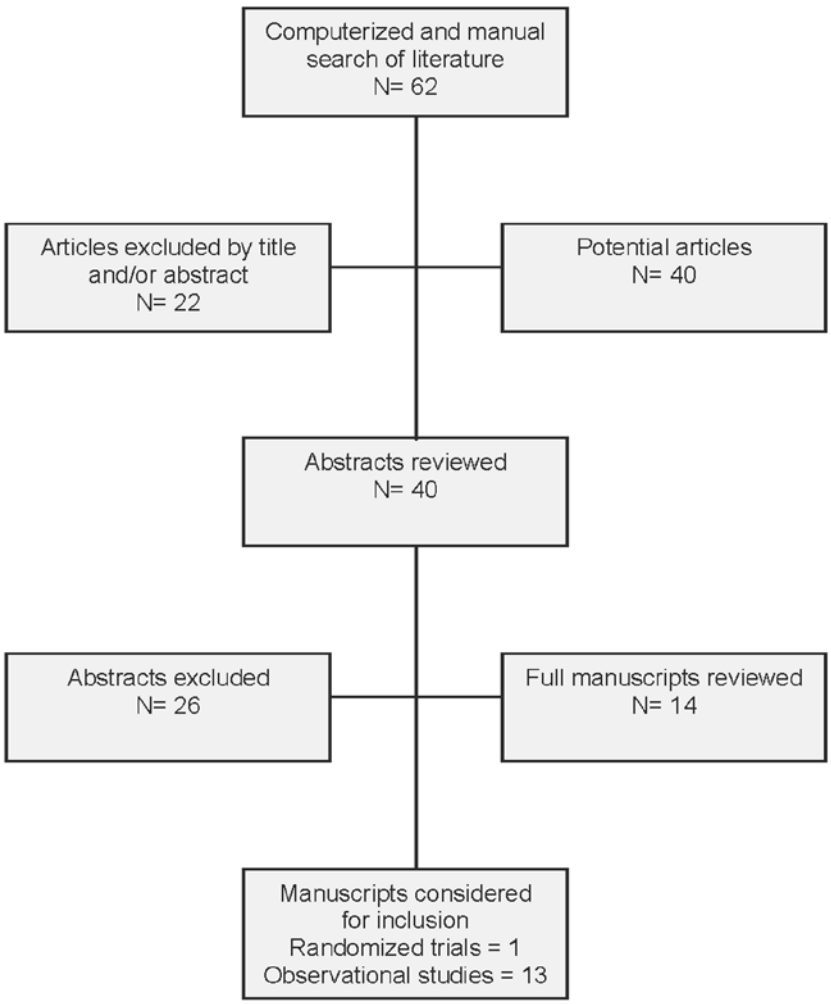

Fig. 1. *Literature search flow diagram illustrating randomized trials and observational studies evaluating outcomes from nucleoplasty.*

(37-50), studying a total of 717 subjects, which met our inclusion criteria and were ultimately included in this systematic review (Fig. 1).

Methodological Quality Assessment

The inclusion and exclusion criteria with the indications and contraindications for nucleoplasty as noted in the reviewed studies are listed in Table 4. Table 5 summarizes the design and methodology of the studies. The Quality Index for each of the included studies and the median score and ranges for each section of the Quality Index are reported in Table 6. Based on methodologic quality standards appropriate for observational reports, the quality of 14 studies was considered excellent (37-50). Only studies that were graded as having excellent methodological quality (Quality Index > 12) were included in the analysis. The Quality Index scale consists of 5 sub-scales: reporting, external validity, internal validity – bias, internal validity – confounding, and power (22). On the first subscale, reporting, the information in the nucleoplasty studies generally provided enough data to allow an assessment of each study's findings. On the subscale of external validity, there was often a lack of evidence that the subjects in the studies were representative of the entire population from which they were derived. For the internal validity – bias subscale, the results were reasonably good with median scores more than half the maximum possible score in this category. However, for the internal validity – confounding subscale, the results were poor, as randomization criteria were not met and the effects of major confounders were often not addressed, such that the median scores were less than half of the maximum possible score. Of note, none of the observational studies in the analysis evaluated the power subscale, which attempts to assess whether the results of the negative findings of the studies could be due to chance.

Study Characteristics and Effectiveness

There was significant heterogeneity in defining the outcome goals among the 14 trials included in this review. The studies used different measures to determine efficacy of nucleoplasty including changes in pain intensity, functional improvement, change in analgesic requirement, and patient satisfaction. This allowed us to perform only a limited subgroup analysis of the results. Table 7 summarizes the various outcome measures for the studies included in our review. Seven articles (38,39,45,47-50) studied the percentage of patients reporting more than 50% pain relief post nucleoplasty

Table 4. *Inclusion and exclusion criteria for studies included in the present review.*

Inclusion/Exclusion criteria	Studies
Inclusion criteria	
Back with or without radicular pain	37,38,41,42,45-47
Leg with or without back pain	39,43
Leg pain > back pain	40
Cervical or unilateral arm pain	44
Radicular or axial low back pain	50
Average pain of at least 5 or greater	48
Failed ≥ 6 weeks of conservative care.	37-50
No neurologic deficit	41,42,47-50
Contained disc herniation	37,39-42,45,47-50
Positive provocative discography	37,40,45-50
Disc height ≥ 75 % of adjacent level	40
Disc height ≥ 50 % of adjacent level	39,42,50
Contained herniated disc <3 mm	44
Contained herniation < 1/5 spinal canal	44
Contained herniation <6 mm	43
Contained herniation ≤5 mm	38
Exclusion criteria	
Sequestered herniation	37,39-42,46-50
Contained herniation > ⅓ spinal canal	37,41,42,46-49
Contained herniation > ½ spinal canal	45
Marked spinal stenosis	37,39-50
Progressive neurological deficits	37,38,41,42,44,46
Tumor	37,38,40-46,50
Infection	36-38,40,42,46-50
Spinal fracture or instability	37,40-50
Heavy opioid usage	42,47-49
Uncontrolled psychological disorders	42,47-50
Litigation.	42,47-49
Negative provocative discography	42,47-49
A loss of > 50% of disc height	37,43,45
A loss of > 30% of disc height	38
Disc height < 25 % of adjacent level	40
1/3 loss of disc height	41,42
Complete annular disruption	40,43
Morbid obesity	37
Spondylolisthesis	37,39,42-44
Previous spinal surgery on the same level	38,42,44,50
Back pain > leg pain	39,43
Coagulopathies	38
Age > 60	39,43
Unstable medical condition	38,39
Large ≥ 6 mm or extruded disc herniation	43
Disc bulges > 5 mm	38
More than 2 symptomatic levels	50
Bone congenital abnormalities	42
Severe degenerative disc material	43

Table 5. Description of included trials.

Study	Description/Design	Sample size	Demographics	Follow-up duration
Sharps et al 2002 (46)	Prospective NR.* Patients meeting I/E** criteria.	N = 49 Single site	53% male • Mean age 38 years Range: 30-61	12 months
Singh et al 2002 (49)	Prospective NR.* Patients meeting I/E** criteria	N = 67 Single site	30% male • Mean age 44 ± 10.6 years Range: 14-62	12 months
Singh et al 2003 (47)	Prospective NR.* Consecutive patients meeting I/E** criteria.	N = 80 Single site	30% male • Mean age 44.8 ± 10.1 years Range: 15-62	12 months
Singh et al 2004 (48)	Prospective NR.* Patients meeting I/E** criteria.	N = 47 Single site	32% male • Mean age 44 ± 11 years Range 15-62	12 months
Reddy et al 2005 (45)	Retrospective NR.* Consecutive patients meeting I/E** criteria.	N = 49 Single site	67% male • Mean age 45 ± 11 years Range: 22-67	> 12 months
Gerszten et al 2006 (40)	Prospective NR.* Patients meeting I/E** criteria.	N = 67 Single site	42% male • Mean age 41 years Range: 21-70	6 months
Bhagia et al 2006 (37)	Prospective NR.* Consecutive patients meeting I/E** criteria.	N = 53 Single site	55% male • Mean age 42.1 ± 13.6 years Range: 17-78	2 weeks
Marin et al 2005 (41)	Prospective NR.* Patients meeting I/E** criteria.	N = 64 Single site	65% male • Mean age 43 ± 9.8 Range: 23-57	12 months
Nardi et al 2005 (44)	Prospective Randomized. Consecutive patients meeting I/E** criteria.	N = 50 Single site	Not reported	Mean 3.8 months Range: 2–9
Cohen et al 2005 (39)	Retrospective NR.* Consecutive patients meeting I/E** criteria.	N = 16 Single site	69% male • Mean age 36.6 ± 7.1 years Range: 22-48	9 ± 5.1 months Range: 4–20
Mirzai et al 2007 (43)	Prospective NR.* Consecutive patients meeting I/E** criteria.	N = 52 Single site	42% male Mean age 44.8 ± 8.6 years	12.1 ± 1.6 months Range: 10–15
Masala et al 2007 (42)	Prospective NR.* Patients meeting I/E** criteria.	N = 72 Single site	67% male • Mean age 48 years Range: 32-64	18 months Range: 12–21
Calisaneller et al 2007 (38)	Prospective NR.* Patients meeting I/E** criteria.	N = 29 Single site	24% male • Mean age 44.14 ± 7.11 years Range: 32-59	6 months
Yakovlev et al 2007 (50)	Retrospective NR.* Patients meeting I/E** criteria.	N = 22 Single site	54.5% male • Mean age 39 years Range: 22-51	12 months

* NR: Non-randomized
** I/E: inclusion/exclusion

Table 6. *Quality Index for included studies.*

Study	Category (maximum possible points in parenthesis)					Quality Index (32)
	Reporting (11)	External Validity (3)	Bias (7)	Confounding (6)	Power (5)	
Sharps et al 2002 (46)	7	1	5	2	0	15
Singh et al 2002 (49)	7	1	5	3	0	16
Singh et al 2003 (47)	10	1	5	3	0	19
Singh et al 2004 (48)	8	1	5	2	0	16
Reddy et al 2005 (45)	7	2	4	2	0	15
Gerszten et al 2006 (40)	6	1	5	2	0	14
Bhagia et al 2006 (37)	8	2	3	2	0	15
Marin 2005 (41)	4	1	4	3	0	12
Nardi et al 2005 (44)	5	2	5	4	0	16
Cohen et al 2005 (39)	8	1	3	2	0	14
Mirzai et al 2007 (43)	8	2	5	2	0	17
Masala et al 2007 (42)	7	2	5	3	0	17
Calisaneller et al 2007 (38)	9	2	5	2	0	18
Yakovlev et al 2007 (50)	8	2	5	2	0	17
Median QI score and range	7.5 (4–10)	1.5 (1–2)	5 (3–5)	2 (2–4)	0 (0–0)	16 (12–19)

(Fig. 2) as determined by changes in pain scores at the time of their final follow-up visit, which ranged from 4 months to >12 months after the procedure. The median percentage of patients with more than 50% pain relief was 53% with a range of 6.25% to 68.2%. Two studies (46,49) reported a 2-point reduction on VAS as their primary outcome measure at the time of the last follow-up visit (Fig. 3). The median percentage of patients with a clinically significant 2-point reduction in pain severity on the VAS scale was 69%, with a range of 59% to 79%. In eleven studies (37-40,42,43,46-50), the baseline pain levels based on VAS values as well as final follow-up values were reported (Table 8), with one study reporting the baseline value and the change in VAS from baseline (45). The median percentage of improvement of VAS from baseline was 38.5% with a range of 11% to 72% (Table 8). The results of pooled VAS scores over time are indicated in Fig. 4. There was a significant difference in pooled VAS scores after nucleoplasty at one, 3, 6 and 12 months follow-up when compared to baseline VAS scores ($P < 0.0001$). Three articles (47-49) reported specific functional improvements in sitting, standing, and walking after nucleoplasty. The percentages of patients reporting improvement in sitting, standing, and walking ability at the time of the last follow-up visit are shown in Fig. 5. The median percentage and range of patients with functional improvement specifically in sitting, standing, and walking at last follow-up were 61% (60–62%), 57% (55–59%), and 54% (49–60%) respectively, although the magnitude of improvement was not reported. One article (41) reported a general 75% improvement in these functions and another study reported that 81.8% of patients had physical functional improvement after nucleoplasty (50). In pooling the results of the various clinical outcomes for pain and function, the median percentage and range of patients meeting any of these success criteria was 62.1% with a range of 6.25% to 84% (Fig. 6).

Level of Evidence

The indicated level of evidence for the nucleoplasty procedure for discogenic pain is Level II-3 based on one randomized trial (44) and 13 (37-43,45-50) observational studies. Using the U.S. Preventive Service Task Force (USPSTF) criteria (35), the evidence for nucleoplasty reflects data obtained primarily from multiple case series utilizing this intervention and describing various outcomes in terms of pain symptoms and function.

Table 7. *Outcome measures of the included studies*

Visual analogue scale	37-43,45-50
Patient satisfaction	39,41,43,45,46
Analgesic use	39,41,43,45,46,50
Return to work	39,41,46
Functional improvement	41,45,47-50
SF-36* and EQ5D** scores	40
Oswestry Scale	43
Pain and symptom relief	43,44
MRI and/or CT scan follow up results	38,42,44
Complications	37,39

* SF-36: Medical Outcomes Study 36-Item Short Form Health Survey
** EQ5D: EuroQol 5D Questionnaire

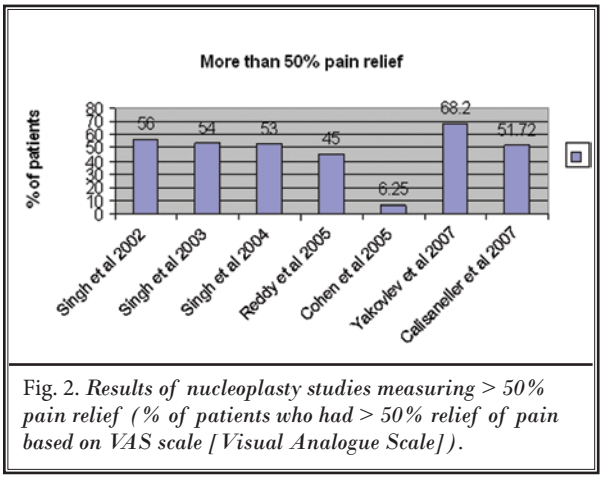

Fig. 2. *Results of nucleoplasty studies measuring > 50% pain relief (% of patients who had > 50% relief of pain based on VAS scale [Visual Analogue Scale]).*

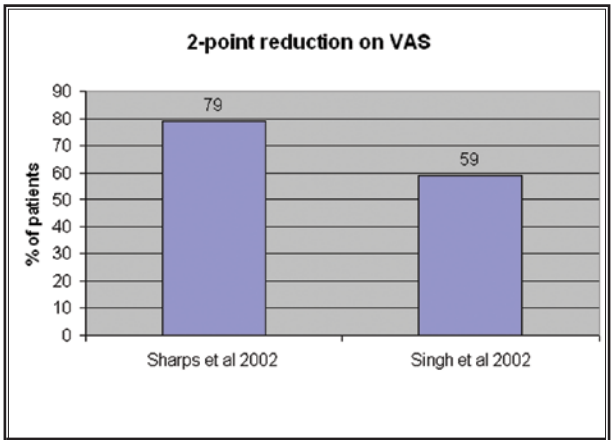

Fig 3. *Results of nucleoplasty studies measuring > 2 point VAS (Visual Analogue Scale) reduction (% of patients who had > 2 point reduction on VAS).*

Table 8. *VAS (visual analogue scale) scores of the included studies*

Study	Baseline VAS	Final follow-up value	Change from baseline value	% Change from baseline
Sharps et al 2002 (46)	7.9	4.3	3.6*	46%*
Singh et al 2002 (49)	6.8	4.1	2.7*	40%*
Singh et al 2003 (47)	6.83	4.5	2.33*	34%*
Singh et al 2004 (48)	6.7	4.4	2.3*	34%*
Reddy et al 2005 (45)	8.08	Not reported	3.67*	45%*
Gerszten et al 2006 (40)	5.4	4.8	0.6	11%
Bhagia et al 2006 (37)	6.74	4.27	2.47*	37%*
Marin 2005 (41)	Not reported	Not reported	Not reported	Not reported
Nardi et al 2005 (44)	Not reported	Not reported	Not reported	Not reported
Cohen et al 2005 (39)	6.7	5.6	1.1	16%
Mirzai et al 2007 (43)	7.5	2.1	5.4*	72%*
Masala et al 2007 (42)	8.2	4.1	4.1*	50%*
Calisaneller et al 2007 (38)	6.95	4.53	2.42*	35%*
Yakovlev et al 2007 (50)	7.6	3.6	4*	53%*

* Statistically significant

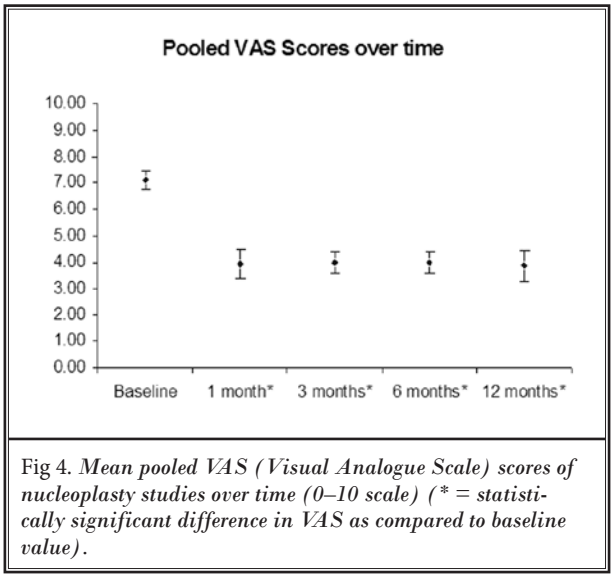

Fig 4. *Mean pooled VAS (Visual Analogue Scale) scores of nucleoplasty studies over time (0–10 scale) (* = statistically significant difference in VAS as compared to baseline value).*

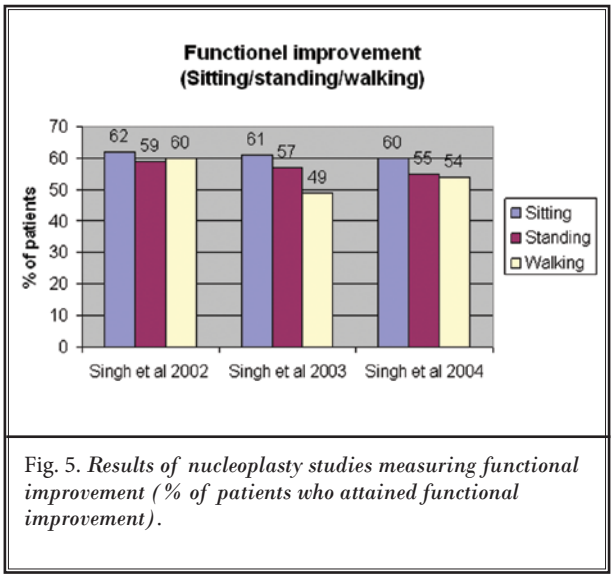

Fig. 5. *Results of nucleoplasty studies measuring functional improvement (% of patients who attained functional improvement).*

Recommendation

This systematic review found that according to Guyatt et al's criteria (36), the recommendation is 1C/strong for the nucleoplasty procedure for discogenic pain. This is based on the methodologic assessment and quality of evidence in grading recommendations that reflect a strong recommendation with moderate to low quality evidence, with benefits outweighing risks, and most evidence coming from observational trials. It is important to note that the evidence must be reconsidered if new evidence becomes available.

Complications

The majority of reviewed studies reported no significant complications related to nucleoplasty (38,40,50).

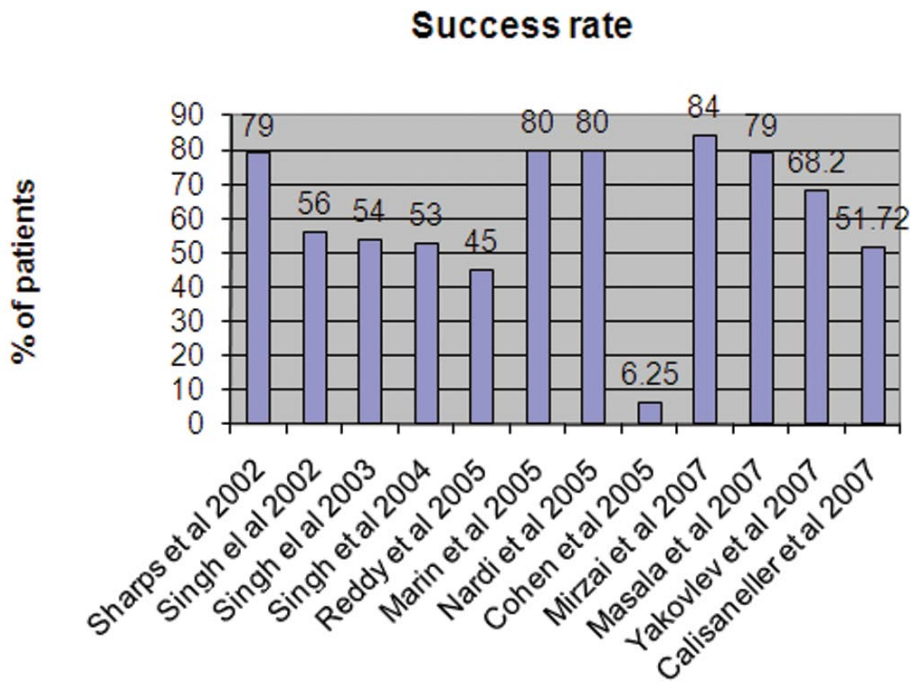

Fig. 6. Results of nucleoplasty studies based on main success criteria (% of patients meeting success criteria).

However, the study by Cohen et al (39) reported that 2 of 16 patients experienced new-onset "neurologic" symptoms following nucleoplasty. One patient complained of numbness in both feet and the other developed twitching symptoms in the leg and back. Bhagia et al (37) performed a quantitative analysis of the incidence of complications following nucleoplasty, specifically investigating short-term effects for up to a 2-week period. In their report, the most common side effects at 24 hours following nucleoplasty were soreness at the needle insertion site (76%), new numbness and tingling (26%), increased intensity of pre-procedure back pain (15%), and new areas of back pain (15%). At 2 weeks following nucleoplasty, all patients had resolution of soreness at their needle insertion site and of pain in new areas of the back. However, new numbness and tingling was present in 15% of patients and 4% of patients had an increased intensity of preprocedure back pain (37). This was not functionally limiting in any of the patients. In each instance, the leg symptoms were non-dermatomal in distribution, suggesting a somatic referral mechanism (51). Symptoms were attributed to provocation of the nerve fibers supplying the posterolateral aspect of the intervertebral disc. One case report of epidural fibrosis following nucleoplasty was reported (52).

Discussion

This systematic review provides a comparative evaluation of clinical outcomes and reported complications for published studies of the nucleoplasty procedure for discogenic back and/or leg pain, isolated low back pain, or cervical and/or arm pain. Although there was significant heterogeneity among the studies, the median percentage and range of patients having successful outcomes after nucleoplasty was 62.1% with a range of 6.25% to 84%. The incidence and severity of reported complications was low.

Except for one study (44), the trials that were included in the present review were observational studies without a control group. Therefore the available literature on nucleoplasty may be confounded by selection and publication bias, limiting the ability to make valid conclusions based upon this data. However, it has been

suggested that well designed cohort or case-controlled studies may provide estimations of therapeutic effect that do not significantly differ from the conclusions of randomized controlled trials (53). The analyzed studies were found to be of adequate methodological quality as judged using the standardized Quality Index assessment checklist (22), a tool that has been previously validated for observational studies.

Based on the Quality Index scale, methodological shortcomings were denoted by the external validity, confounding, and power subscales which reduced the quality rating of the 14 analyzed studies. However, based on the entirety of the analysis, the overall median quality index score was 16 (of a maximum possible score of 32). This score is above the quality score of 12 that is acknowledged as denoting excellent methodological quality for observational studies. In our review, we excluded studies with scores less than 12 (24). As our analysis shows, the trials included in this review were methodologically sound; however, there remains room for improvement in the quality of studies that can be done for nucleoplasty.

A number of limitations are noted in reviewing the literature and may have affected the results of our analysis. Publication bias may exist, as only studies with positive findings may have been put forth. One potential reporting issue with the studies in our review is that 3 of the published reports were by the same primary author and represented the results of a single center (47-49). Therefore, these results may be affected by site-specific bias. However, the outcomes reported for this same-site practice are comparable to the results from other practitioners. There is significant heterogeneity of trial design among the reports, differences in inclusion criteria, varied patient populations, and differing techniques and experience of the clinicians performing the procedure. Also, there are different time periods used as end-points for assessing outcome. Three studies looked at return to work as an outcome criteria (39,41,46). Six studies looked at patient function rather than pain as a primary outcome (41,45,47-50). In 2 articles (37,45), patients who had nucleoplasty also had paravertebral steroids injected at the time of their procedure. In one study (44), the results are reported for cervical spine nucleoplasty rather than lumbar. Although several of the studies used uncontrolled psychological disorders as exclusion criteria, none of the studies reported whether psychological factors, disability claims, or the presence of a pending lawsuit affected the results of the procedure. There was no relationship noted between results and gender or age that suggested higher or lower success or complications. The heterogeneity of outcomes and reported data made it difficult to perform any kind of pooled retrospective analysis on these criteria and to determine whether these factors correlated with a good or bad outcome. Nevertheless, for each subgroup, data were statistically pooled based on the outcome criteria that were being evaluated. Review of these reports indicated a diversity of criteria that was used to determine inclusion into each study, but with all patients having discogenic back pain as their primary reason for undergoing nucleoplasty. In evaluating the available studies, we believe that differences in inclusion criteria followed a random effects model, such that although the effects studied in each study were not identical, they represented a typical distribution of differences among patients as may be seen in a typical clinical practice. Therefore, because these potential confounding variables are randomly allocated among studies, the outcomes reported represent an average of impact of these events. Because the types of patients studied in the various reports are representative of a typical clinical practice, the results were felt to be valid and to reflect clinically relevant outcomes for nucleoplasty. Based on the overall quality of the 14 studies, as evaluated by the Quality Index tool, we felt that it would be valid to use the results of all of the articles to calculate an overall effectiveness based on the success criteria identified in each of the studies.

Patient selection criteria are a significant source of heterogeneity in the reviewed trials. In selecting subjects for nucleoplasty, the actual anatomy of the degenerated disc may be important. Reports suggest that patients with large annular fissures may be unlikely to benefit from nucleoplasty even in a setting of a disc herniation that is "contained," and patients with incomplete annular tears and minimally degenerated discs can be expected to benefit most (21). Furthermore, a higher intensity of leg pain more than axial back pain in the presence of a contained herniated disc is thought to be a strong indication for nucleoplasty. Some studies suggest that patients who have only back pain will have poor results (39). Discography was described as being utilized in 11 of the 14 analyzed trials of patients who underwent nucleoplasty (37,39,40,42,43,45-50). In 6 studies, axial pain was present without radicular symptoms (37,40,46-49), in 4 studies patients had both axial and radicular pain (39,42,45,50), and in one study patients had predominantly radicular pain (43). Proper patient selection is a key element for successful nucleo-

plasty and future well-configured trials will need to differentiate which patients may benefit most from this procedure.

An outlying report on nucleoplasty is presented by Cohen et al (39), which reported only a 6.25% success rate. Some of the reasons for these negative findings can be attributed to selection criteria that did not exclude patients with severe annular tears, as would be evidenced by preoperative discography, or with moderately degenerated discs. The study was retrospective in design, used data from telephone follow-ups at variable times following the procedure, and was conducted using military personnel during a time of war. Other potential confounding factors were present, since 9 of 16 patients had undergone IDET prior to nucleoplasty, 4 of 7 patients who had nucleoplasty alone had a 2-level procedure done, and only 8 patients had "contained" herniations. Half of the patients had non-contained annular tears as evidenced by preoperative discography, with extravasation of contrast material into the epidural space. Singh et al (48) commented on the degree of annular disruption and its significant impact on long-term outcome following disc decompression. A higher level of annular disruption or disc degeneration may result in a poorer prognosis following nucleoplasty. The excess severity of disease in these groups may have negated the effects of nucleoplasty on reducing pain or improving function.

In our analysis, we were able to perform a limited meta-analyses based on improvement in VAS scores after nucleoplasty. We performed smaller subgroup analysis based on other outcome criteria. There was a significant difference in pooled VAS scores after nucleoplasty at one, 3, 6, and 12 months follow-up as compared with baseline pooled VAS score ($P < 0.0001$). With the exception of Cohen's study (39), 45% to 84% of patients had a successful procedural outcome at the time of their final evaluation after the procedure. Even with Cohen's outlying study that reported only a 6.25% success rate (1/16 patients), the median percentage of improvement in VAS scores from baseline is 38.5% (range: 11–72%). Gertszen et al (40) did not demonstrate a decrease in VAS scores after nucleoplasty, but clinical improvement in other outcome measures was found, as demonstrated by improved scores on the SF-36 (Medical Outcomes Study 36-Item Short Form) Health Survey and EQ5D (Euro Quality of Life 5 D). The investigators reported that patients' strength and function improved and remained improved following nucleoplasty despite a return of pain. They concluded that nuceloplasty is safe and appears to improve overall quality of life (40).

Bhagia et al (37) demonstrated relatively small changes in postprocedure VAS scores 2 weeks after nucleoplasty, achieving VAS reductions of 2.47 (back pain), 1.55 (right leg pain), and 2.62 (left leg pain). Their study design did not distinguish between patients who had axial pain or radicular pain and was primarily intended to identify potential complications after this procedure. Patients were assessed for only 2 weeks after the procedure.

Nucleoplasty may be less effective for patients with discogenic low back pain without radicular symptoms. Singh et al (48) studied the effectiveness of nucleoplasty for this group of patients and demonstrated only a modest 34% reduction in VAS scores. However, while some practitioners (39) believe that nucleoplasty is not the correct procedure for patients with only discogenic, axial low back pain, others (48) feel that nucleoplasty can help these patients as well. Nucleoplasty may reduce axial pain since it denervates the central end-plate area of the disc, which is where innervation is most concentrated (54). Furthermore the radiological findings after nucleoplasty described by Calisaneller et al (38) suggest that the pain relieving effect can be due to immediate reduction in the intradiscal pressure and/or nociceptive ablative effect of coblation on the nerve fiber network innervating the annulus fibrosus.

Similar to other interventional spine procedures, careful patient selection for nucleoplasty is necessary to achieve successful outcomes. Cohen et al (39) recommended that candidates for nucleoplasty have predominantly radicular pain and that symptoms are confirmed by selective nerve root blocks or electromyography/nerve conduction studies. The disc protrusion should be < 6 mm in size and there should be a functionally intact outer annulus as determined by CT discography. Singh et al (48) recommended utilizing strict inclusion criteria especially for patients suffering with only low back pain. Prior to nucleoplasty, these patients were required to have a positive provocative discography test and fail conservative management, including fluoroscopically directed epidural steroid injections. Radiographic findings alone were not the sole determination of pain origin and for patient inclusion.

Although 12 of the 14 analyzed clinical trials reported no major complications related to nucleoplasty (38,40-50) it is likely this procedure carries the risks and side effects of procedures that are technically similar, including the risks of bleeding, infection, and neurological damage. Initial effects such as soreness at the

needle insertion site and back pain generally resolve within 2 weeks (37). Numbness and tingling in the legs and feet and twitching in the leg and back have been reported to persist but do not seem to be functionally limiting (39). Further quantitative studies assessing the incidence and duration of side effects and complications following nucleoplasty will need to be conducted to understand the risks of this procedure.

Conclusion

The results of this systematic review evaluating outcomes following the nucleoplasty procedure for discogenic pain have been based on Level II evidence showing pain relief and improved functional outcomes. The nucleoplasty procedure has a I-C/strong recommendation that it improves outcomes in certain patients as a treatment for discogenic pain. This systematic review has shown, however, that the majority of the literature on nucleoplasty reflects the results of observational studies.

Our results are similar to those reported in a previous systematic review on the nucleoplasty procedure (9), even though the 2 reviews used different methodological quality assessment scales. However, based on dissimilar opinions on the relative benefit vs risk of the procedure, the two reviews offer variable recommendations.

The initial studies on nucleoplasty are encouraging and suggest that it may be a viable minimally invasive percutaneous therapeutic option. However, well-designed, methodologically sound trials are lacking. Weaknesses in the studies examined include the possibility of selection bias, publication bias, heterogeneity of inclusion criteria and outcome measures, and timing of outcomes. All but one of the publications in the pooled analysis were non-randomized and all were unblinded studies, perhaps reflecting on the general difficulty of conducting placebo-controlled randomized trials of invasive procedures. Although the Quality Index tool is an accepted way of judging the quality of observational studies, some may be skeptical about pooling the results of various studies with different outcome criteria. In order to more definitively prove that the nucleoplasty procedure leads to improved pain and functional outcomes, more higher quality studies are needed.

Future areas of research will need to determine which selection criteria predict the best outcomes of this procedure. In evaluating the results after nucleoplasty, study design needs to take into account the natural history of discogenic pain, which may improve with conservative treatment or no treatment, as well as issues such as regression to the mean and the placebo response in determining whether improvement in pain is actually due to this treatment. Therefore, we advocate for either well designed case-controlled trials or, if possible, randomized, controlled trials in order to compare nucleoplasty with open surgical procedures or other interventional techniques for treating discogenic back pain. Better designed studies should also examine what medical and psychological factors predict success in both pain reduction and functional improvement from this procedure.

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