

Surgical Interventions for Lumbar Disc Prolapse

Updated Cochrane Review

J. N. Alastair Gibson, MD, FRCS, and Gordon Waddell, DSc, MD, FRCS

Study Design. An updated Cochrane Review.

Objectives. To assess the effects of surgical interventions for the treatment of lumbar disc prolapse.

Summary of Background Data. Disc prolapse accounts for 5% of low back disorders yet is one of the most common reasons for surgery. There is still little scientific evidence supporting some interventions.

Methods. Use of standard Cochrane review methods to analyze all randomized controlled trials published up to January 1, 2007.

Results. Forty randomized controlled trials (RCTs) and 2 quasi-RCTs were identified. Many of the early trials were of some form of chemonucleolysis, whereas the majority of the later studies either compared different techniques of discectomy or the use of some form of membrane to reduce epidural scarring. Four trials directly compared discectomy with conservative management, and these give suggestive rather than conclusive results. However, other trials show that discectomy produces better clinical outcomes than chemonucleolysis, and that in turn is better than placebo. Microdiscectomy gives broadly comparable results to standard discectomy. Recent trials of an interposition gel covering the dura (5 trials) and of fat (4 trials) show that they can reduce scar formation, although there is limited evidence about the effect on clinical outcomes. There is insufficient evidence on other percutaneous discectomy techniques to draw firm conclusions. Three small RCTs of laser discectomy do not provide conclusive evidence on its efficacy. There are no published RCTs of coblation therapy or transforaminal endoscopic discectomy.

Conclusion. Surgical discectomy for carefully selected patients with sciatica due to lumbar disc prolapse provides faster relief from the acute attack than conservative management, although any positive or negative effects on the lifetime natural history of the underlying disc disease are still unclear. The evidence for other minimally invasive techniques remains unclear except for chemonucleolysis using chymopapain, which is no longer widely available.

Key words: automated percutaneous discectomy, chymopapain, Cochrane Review, disc prolapse, endoscopic, laser, randomized controlled trial, surgery. **Spine 2007;32:1735–1747**

Lumbar disc prolapse (“slipped disc”) accounts for less than 5% of all low back problems but is the most common cause of nerve root pain (“sciatica”). Ninety percent of acute attacks of sciatica settle with conservative management. Absolute indications for surgery include altered bladder function and progressive muscle weakness, but these are rare. The usual indication for surgery is to provide more rapid relief of pain and disability in the minority of patients whose recovery is unacceptably slow.

The primary rationale of any form of surgery for disc prolapse is to relieve nerve root irritation or compression due to herniated disc material, but the results should be balanced against the likely natural history. Surgical planning should also take account of the anatomic characteristics of the spine and any prolapse,¹ the patient’s constitutional makeup, and equipment availability. Of the techniques available, open discectomy, performed with (micro-), or without the use of an operating microscope, is the most common, but there are now a number of other less invasive surgical techniques. Ideally, it would be important to define the optimal type of treatment for specific types of prolapse.² For example, different surgical procedures may be appropriate if disc material is sequestered rather than contained by the outer layers of the anulus fibrosus, and the choice of treatment should reflect these.

Many of the early trials relate to the use of chemonucleolysis (dissolution of the nucleus by enzyme injection) using chymopapain. Chemonucleolysis became popular in the 1970s after its introduction as a therapy for a contained lumbar disc prolapse, *i.e.*, without fragment sequestration into the spinal canal.³ Concerns about its safety and controversy about its effectiveness led to it being withdrawn for a while by the U.S. Food and Drug Administration, but it was rereleased in 1982. Its use is currently in decline, so this is an appropriate time to synthesize the evidence on its effectiveness.

There are several nonsystematic reviews that consider the relative merits of microdiscectomy, automated percutaneous discectomy, and various types of arthroscopic microdiscectomy. In all these treatments, smaller wounds are said to promote faster patient recovery with earlier hospital discharge,^{4–6} but the question remains whether that is actually associated with improved clinical outcomes. RCTs are required to provide Level 1 evi-

From the Spinal Unit, Royal Infirmary of Edinburgh and the University of Edinburgh, Edinburgh, Scotland.

Supported by the Medical Research Council, UK.

This paper is based on Gibson JNA, Waddell G. Surgical interventions for lumbar disc prolapse. Cochrane Database of Systematic Reviews 2007, Issue 2, a Cochrane Review published in The Cochrane Library 2007, Issue 2 (www.thecochranelibrary.com). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Library should be consulted for the most recent version of the review.

The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication.

Federal funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Address correspondence and reprint requests to J. N. Alastair Gibson, MD, FRCS, Royal Infirmary of Edinburgh, Little France, Edinburgh, EH16 4SU, UK; E-mail: j.n.a.gibson@blueyonder.co.uk

dence of treatment efficacy. Moreover, treatment may prove to be of marginal benefit yet expensive and hence not cost-effective. It is particularly important that the safety, efficacy, and cost benefits of all new innovative procedures should be compared with currently accepted forms of treatment.

Objectives

We aimed to test the following null hypotheses. In the treatment of lumbar intervertebral disc prolapse, there is no difference in effectiveness or incidence of adverse complications between:

1. Any form of discectomy and conservative management
2. Microdiscectomy and open "standard" discectomy
3. Forms of minimally invasive therapy, including automated percutaneous discectomy, laser discectomy, percutaneous endoscopic discectomy, transforaminal endoscopic discectomy, and microdiscectomy
4. Chemonucleolysis and placebo injection
5. Chemonucleolysis and discectomy
6. Discectomy with and without materials designed to prevent postoperative scar formation

Criteria for Considering Studies for This Review

Types of Studies. All randomized controlled trials (RCTs) or quasi-RCTs (QRCTs, methods of allocating participants to a treatment that are not strictly random, *e.g.*, by date of birth, hospital record number, or alternation) pertinent to the surgical management of lumbar disc prolapse.

Types of Participants. Patients with lumbar disc prolapse who have indications for surgical intervention.

Where possible, an attempt was made to categorize patients according to their symptom duration (<6 weeks, 6 weeks to 6 months, >6 months) and by their response to previous conservative therapy. We included studies comparing methods of treatment of any type of lumbar disc prolapse and searched carefully for any data relating to specific types of prolapse (for example, central, lateral, far-out, sequestered).

Types of Interventions. Data were sought relating to the use of discectomy, microdiscectomy, chemonucleolysis, automated percutaneous discectomy, nucleoplasty, and laser discectomy. Any modifications to these interventional procedures were included, but alternative therapies such as nutritional or hormonal therapies were excluded.

Types of Outcome Measures. The following outcomes were sought:

- A) Patient-centered outcomes
 - i) Proportion of patients who recovered according to self, a clinician's assessment or both
 - ii) Proportion of patients who had resolution or improvement in pain

- iii) Proportion of patients who had an improvement in function measured on a disability or quality of life scale
- iv) Return to work
- v) Economic data as available
- vi) Rate of subsequent back surgery

- B) Measures of objective physical impairment

Spinal flexion, improvement in straight leg raise, alteration in muscle power, and change in neurologic signs.
- C) Adverse complications
 - i) *Early*: Damage to spinal cord, cauda equina, dural lining, a nerve root, or any combination; infection; vascular injury (including subarachnoid hemorrhage); allergic reaction to chymopapain; medical complications; death
 - ii) *Late*: Chronic pain, altered spinal biomechanics, instability or both; adhesive arachnoiditis; nerve root dysfunction; myelocoele; recurrent disc prolapse
- D) Cost data

Search Strategy for Identification of Studies

Relevant published data from randomized controlled trials in any language, up to January 1, 2007, were identified by the following search strategies:

1. Computer aided searching of MEDLINE⁷ with specific search terms and PUBMED (www.ncbi.nlm.nih.gov/)
2. Personal bibliographies
3. Hand searching of *Spine* and meeting abstracts of most major spinal societies from 1985
4. Cochrane Central Register of Controlled Trials
5. Communication with members of the Cochrane Back Review Group and other international experts
6. Citation tracking from all papers identified by the above strategies

The International Standard Randomized Controlled Trial Number Register and Clinical Trials Register were searched from their beginning to September 20, 2006 to identify ongoing studies (<http://www.controlled-trials.com/>; clinicaltrials.gov).

Methods of the Review

Eligible trials were entered into RevMan 4.2 and sorted on the basis of the inclusion and exclusion criteria. For each included trial, assessment of methodologic quality and data extraction were carried out as detailed below.

1. Two review authors (J.N.A.G., G.W.) selected the trials to be included in the review. Disagreement was resolved by discussion, followed if necessary by further discussion with an independent colleague.
2. The methodologic quality was assessed and internal validity scored by the review authors, assessing

risk of preallocation disclosure of assignment, intention-to-treat analysis, and blinding of outcome assessors.⁸ The quality of concealment allocation was rated in 3 grades: A: clearly yes, some form of centralized randomization scheme or assignment system; B: unclear, assignment envelopes, a “list” or “table,” evidence of possible randomization failure such as markedly unequal control and trial groups, or trials stated to be random but with no description; C: clearly no, alternation, case numbers, dates of birth, or any other such approach, allocation procedures that were transparent before assignment. Withdrawal, blinding of patients and observers, and intention-to-treat analyses were assessed according to standard Cochrane methodology and tabulated in the results tables.

The nature, accuracy, precision, observer variation, and timing of the outcome measures were tabulated. Initially, any outcomes specified were noted. The data were then collated and the most frequently reported outcome measures (in 5 or more studies) used for meta-analysis. Indeed, only 3 outcomes were consistently reported: the patient’s rating of success, a surgeon’s rating of success, and the need for a second procedure (treatment failure). To pool the results, ratings of excellent, good, and fair were classified as “success” and poor, unimproved, and worse as “failure.” The pooled data are given in the analysis table.

3. For each study, odds ratios (ORs) and 95% confidence limits (95% CI) were calculated. Results from clinically comparable trials were pooled using random effects models for dichotomous outcomes. It should be noted that, in several instances, the test for heterogeneity was significant, which casts doubt on the statistical validity of the pooling. Nevertheless, there is considerable clinical justification for pooling the trials in this way; and in view of the clinical interest, these results are presented as the best available information at present, with the qualification that there may be statistical weaknesses to the results.

Description of Studies

Forty-two studies have been included in this review as detailed below. Details of individual trials are presented in Table 1.

Methodologic Quality of Included Studies

Many of the trials, particularly of surgery, had major design weaknesses. Some of the trials were of a very small number of patients. Methods and published details of randomization were often poor, and there was lack of concealment of randomization. Because of the nature of surgical interventions, double blinding was not possible. Blinded assessment of outcome was generally feasible yet often not even attempted. There were few proper clinical outcomes,⁹ and the most common surgical out-

comes were crude ratings by patients or surgeons. Some of the assessments were by the operating surgeon or by a resident or fellow beholden to the primary investigator. Although 35 of the trials had follow-up rates of at least 90%, there was often considerable early code break or crossover of patients, which was not always properly allowed for in the analysis or presentation of results. Only 10 of the 42 trials presented 2-year follow-up results as recommended for surgical studies, although 2 of these trials also presented 10-year results.

These defects of trial design introduced considerable potential for bias. Most of the conclusions of this review are based on 6- to 12-month outcomes, and there is a general lack of information on longer-term outcomes.

Results

Forty RCTs and 2 QRCTs are included in this updated review. This an increase of 15 reports over the first edition of the review (1998), but 17 new papers are actually included, as 2 were deleted from the original set^{10,11} due to a lack of publication of substantive results within a 5-year period. One additional new abstract was excluded for the same reason.¹² Sixteen of the original trials were found on MEDLINE, 5 by searching on-line OVID, and the final 6 by hand-searching conference proceedings and personal bibliographies and correspondence with experts. The new trials were mainly collected by the authors from personal literature review or after notification by colleagues from the Cochrane Back Review Group. Nine additional trials are currently labeled “ongoing” as insufficient data are available to allow critical analysis.

It was not possible to analyze patients according to duration of their symptoms, previous conservative treatment, type of disc prolapse, or indications for surgery, as few of the trials provided these data in usable form. Many trials provided limited information on selected complications, but these were not comparable between trials. Moreover, relatively small RCTs do not have sufficient statistical power to produce any meaningful conclusions about complications of low incidence. That requires a completely different kind of database, which is much larger and more representative of routine clinical practice.¹³

Five studies attempted to estimate costs,^{14–18} and 3 of these estimated cost-effectiveness,^{16–18} although their methodology has been criticized.¹⁹

Discectomy

There are now 4 trials included in the review comparing surgical treatment of lumbar disc prolapse with some form of natural history, conservative treatment, or placebo, but one of these is still only published as an abstract.²⁰ In the first trial, Weber²¹ compared long-term outcomes of treatment by discectomy *versus* initial conservative management followed by surgery if conservative therapy failed. The trial was not blinded and 26% of the “conservative” group actually came to surgery, *i.e.*,

Table 1. Included Studies

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Benoist (1993) ⁴⁶	Independently generated list blinding: double; lost to follow-up: 34 of 118 at 1 yr	Paris, France; 118 patients; 80 male, 8 female; age 21–70 yr; lumbar disc herniation + radicular pain; unsuccessful conservative treatment (6 wk)	Experimental: chymopapain (2000 U); control: chymopapain (4000 U)	Surgeon rating; patient rating at 1 yr		B
Bernsmann (2001) ⁵⁴	Randomization method not stated; blinding: double; lost to follow-up: 14 of 200 at 2 yr	Bochum, Germany; 200 patients; 97 male, 89 female; age 22–75 yr	Experimental: fat graft; control: no fat graft	Patient rating at 2 yr		B
Bontoux (1990) ⁴⁹	Table randomization; blinding: assessor; lost to follow-up: 0 of 80 at 6 mo	Poitiers, France; 80 patients; sciatica for 2 mo	Experimental: chymopapain (4000 U); control: triamcinolone hexacetone (70 mg)	Independent observer rating; 2nd procedure required at 6 mo	French translation	A
Bourgeois (1988) ⁴⁸	Drawing of lots; blinding: double; lost to follow-up: 0 of 60 at 6 mo	Paris, France; 60 patients; 40 male, 20 female; age 26–62 yr; sciatica for 6 wk	Experimental: chymopapain (4000 U); control: triamcinolone hexacetone (80 mg)	Independent observer rating; 2nd procedure required at 6 mo	French translation	C
Bromley (1984) ⁵⁰	Table randomization; blinding: double; lost to follow-up: 0 of 30 at 17 mo	Paterson, NJ; 30 patients; 15 male, 15 female; age 21–63 yr; failed conservative therapy (including 2-wk bed rest); myelogram: confirming a single herniated disc	Experimental: collagenase (600 U/mL); control: normal saline	Patient rating at 17 mo		A
Butterman (2004) ²³	Computer randomization; blinding: nil; lost to follow-up: 3 of 100	Stillwater, MN 100 patients; large herniations (>25% cross section of spinal canal) with failure of conservative treatment after 6 wk	Experimental: discectomy; control: epidural steroid (up to 3 weekly injections)	Back and leg pain ODI; 2nd procedure required at 3 yr	Steroid dose and use of fluoroscopy varied	A
Chatterjee (1995) ¹⁶	Randomization method not stated; blinding: assessor; lost to follow-up: 0 of 71 at 6 mo	Liverpool, UK; 71 patients; 39 male, 32 female; age 20–67 yr; contained disc herniation at a single level; unsuccessful conservative treatment (minimum 6 wk)	Experimental: automated percutaneous lumbar discectomy; control: microdiscectomy	Repeat surgery (microdiscectomy) required following failed APLD; independent observer rating at 6 mo	Parallel study of direct/social economic costs reported in different publication (Stevenson, 1995)	B
Crawshaw (1984) ⁴⁴	Randomization method not stated; blinding: nil; lost to follow-up: 2 of 52 at 1 yr	Nottingham, UK; 52 patients; age 15–60 yr; root involvement at a single level; failed conservative treatment (minimum 3 mo)	Experimental: chemonucleolysis (4000 U chymopapain); control: surgery (choice left to surgeon)	Surgeon rating; 2nd procedure required at 1 yr		B
Dabiez (1988) ⁴²	Randomization method not stated; blinding: double; lost to follow-up: 9 of 173 at 6 mo	Multicenter, US (25 centers) 173 patients; 112 male, 61 female; age 18–70 yr; proven classic lumbar disc syndrome with unilateral single-level radiculopathy; failed conservative treatment (minimum 2-wk strict bed rest)	Experimental: chymopapain (8 mg in 2 mL); control: cysteine-edetate-ithalamate	Surgeon rating; 2nd procedure required at 6 mo		A
De Tribolet (1998) ⁵⁶	Randomization by computerized paradigm; blinding: double; lost to follow-up: 31 of 298 at 6 mo	Lausanne, Switzerland; 298 patients; 167 male, 102 female; mean age 39 yr; single-level disc prolapse	Experimental: Adcon-L gel; control: no anti-adhesion gel	Postoperative scarring on MRI scan; 2nd procedure; radicular pain at 6 mo	European arm of Adcon-L study; some patients had a laminectomy (6) or hemilaminectomy (102)	A
Ejeskar (1983) ⁴³	Randomization method not stated; blinding: assessor; lost to follow-up: 0 of 29 at 1 yr	Gothenburg, Sweden; 29 patients; 22 male, 7 female; age 19–73 yr; obvious signs + symptoms of a herniated disc; severe symptoms for longer than 4 mo positive myelogram	Experimental: chymopapain (4000 IU) control: surgery (laminotomy)	Patient rating; 2nd procedure required at 1 yr		B

(Continued)

Table 1. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Feldman (1986) ⁴¹	Drawing of lots; allocation concealment: B; blinding: double; lost to follow-up: 0 of 39	Paris, France; 39 patients; symptoms resistant to 4 wk conservative therapy	Experimental: chymopapain (4000 U) control: distilled water	Independent observer assessment; reoperation at 22 mo	French translation	B
Fraser (1982) ³⁹	Randomization method not stated; blinding: double; lost to follow-up: 0 of 60 at 2 yr, 4 of 60 at 10 yr	Adelaide, Australia; 60 patients; 39 male, 21 female; age 19–69 yr; failed conservative treatment (unknown duration) within preceding 6 mo; myelogram demonstrating posterolateral herniated disc at single level	Experimental: chymopapain (8 mg in 2 mL); control: saline (2 mL)	Surgeon rating; patient rating; 2nd procedure required at 2, 10 yr	6 mo, 2 yr, and 10 yr follow-up: reported in separate publications	A
Gambardella (2005) ⁵⁵	Randomization method not stated; radiologist blinded; lost to follow-up: 2 of 74	Messina and Reggio Calabria, Italy; 74 patients	Experimental: fat graft; control: nil	Surgeon's assessment of clinical score; radiologic score	1 yr	B
Geisler (1999) ¹⁸	Closed envelope randomization; blinding: single + assessor; lost to follow-up: Europe, 29 of 298; US, 45 of 268	Multicenter, Europe (9 centers); 298 patients; 167 male, 102 female; followed-up; mean age, 38 yr; multicenter, US (16 centers) 268 patients; male: female not specified	Experimental: ADCON-L anti-adhesion barrier gel; control: nil	Patient rating, MRI scar score at 6 mo	US arm of Adcon-L study; figures submitted to FDA by manufacturer falsified	A
Greenfield (2003) ²⁰	Closed opaque envelope randomization; blinding: nil; lost to follow-up: 0 of 88	Bristol, UK; 88 patients; 50 male, 38 female; small or moderate lumbar disc herniation	Experimental: microdiscectomy; control: physiotherapy exercises	VAS ODI; work loss at 2 yr		A
Haines (2002) ³³	Randomization not stated; lost to follow-up: 8 of 35 at 6 mo	Multicenter, US (8 centers); 35 patients; 19 male, 16 female	Experimental: automated percutaneous discectomy; control: conventional discectomy	Surgeon rating; SF-36 Roland score at 1 yr	37 patients recruited of 5735 screened and 95 eligible	B
Hedtmann (1992) ⁴⁷	Randomization by drawn cards; blinding: nil; lost to follow-up: 16 of 100 at 5 yr	Bochum, Germany; 100 patients; 65 male, 35 female; contained disc at 1 level; failed conservative treatment (minimum 6 wk)	Experimental: collagenase 400 ABC U; control: chymopapain (4000 U)	Surgeon rating 1 yr, 5 yr; 2nd treatment required 3 yr, 5 yr	5 year results included in separate publication (Wittenberg <i>et al</i> , 1996)	B
Henriksen (1996) ²⁷	Closed envelope randomization; blinding: single; no losses to follow-up	Copenhagen, Denmark; 79 patients; age 30–48 yr; single level nerve root compromise	Experimental: microsurgical discectomy; control: standard lumbar discectomy	Back pain score, leg pain score, time to discharge at 6 wk		A
Hermantin (1999) ²⁹	Closed envelope randomization; blinding: nil; lost to follow-up: 0 of 60	Philadelphia, PA; 60 patients; age 15–67 yr; single intracanal herniation <50% AP canal diameter	Experimental: arthroscopic microdiscectomy; control: laminotomy and discectomy	Days to return to normal activity; mean pain score; Patient rating at 2 yr		B
Huang (2004) ⁹⁰	Randomization method not stated; blinding: uncertain; lost to follow-up: not mentioned	Chengdu Sichuan, China; 62 patients; 37 male, 25 female; age 29–71 yr	Experimental: polylactic acid membrane; control: Nil	Surgeon rating		B
Huang (2005) ²⁸	Randomization method not stated (1 of 22 not randomized); blinding: nil; no losses to follow-up: at 19 mo	Putz city, Taiwan; 22 patients; age 39 ± 11 yr	Experimental: microendoscopic discectomy; control: open discectomy	Patient satisfaction; hospital stay; blood loss; skin incision length; cytokine responses at 19 mo		B

(Continued)

Table 1. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Javid (1983) ⁴⁰	Randomization from permuted blocks; blinding: double; lost to follow-up: 2 of 108 at 6 mo	Multicenter, US (7 centers); 108 patients; 63 male, 45 female; age 36 to 41 yr; period of study: 1981–1982; positive myelogram for single disc herniation; failed conservative treatment (minimum 6 wk)	Experimental: chymopapain (3000 U); control: sterile saline solution	Patient rating; physician rating; 2nd procedure required; code break at 6 mo		A
Jensen (1996) ⁵³	Randomization method not stated; blinding: single + assessor; 9 of 118 lost to follow-up	Hilleroed, Denmark; 118 patients; 53 male, 46 female; age 19–75 yr; myelogram or CT verified disc prolapse	Experimental: implantation of free fat graft following discectomy; control: nil following discectomy	Patient assessment CT at 1 yr		B
Kim (2004) ⁵⁸	Computer-generated randomization (2:1); blinding: single; lost to follow-up: 1 of 18	Multicenter, US (6 centers); 18 patients; 7 male, 11 female	Experimental: Oxiplex/SP gel; control: surgery alone	Lumbar spine outcomes questionnaire at 1 yr		A
Krugluger (2000) ³²	Randomization method: not stated; lost to follow-up: 7 of 29	Vienna, Austria; 22 patients; 16 male, 6 female; age 24–60 yr; contained herniated disc with neurologic deficit	Experimental: automated percutaneous discectomy; control: chemo-nucleolysis 4000 IU chymodiactin	Secondary surgery at 2 yr		B
Lagarigue (1994) ²⁶	Drawing of lots; blinding: assessor; lost to follow-up: 0 of 80 at 15 mo	Toulouse, France; 80 patients; disc hernia treated conservatively for 3 mo	Experimental: micro-discectomy; control: discectomy	Surgeon rating at 15 mo	French translation	B
Lavignolle (1987) ¹⁴	Randomization method not stated; blinding: nil; lost to follow-up: 0 of 358 at 2 yr	Bordeaux, France; 358 patients; hernia without major neurologic deficit	Experimental: chemonucleolysis (4000 U); control: discectomy with magnification	Surgeon rating; independent observer rating; 2nd procedure required; cost analysis at 2 yr	French translation	B
MacKay (1995) ⁵²	Randomization method not stated; blinding: assessor; lost to follow-up: 36 of 154	Royal Oak, MI; 154 patients; 106 male, 48 female; age 14–79 yr; radiographically proven single-level herniation; unsuccessful nonoperative treatment (minimum 6 wk)	Experimental: free-fat graft/Gelfoam; control: nil	Independent observer assessment; MRI scar formation at 1 yr		A
Mayer (1993) ³⁴	Randomization method not stated; blinding: nil lost to follow-up: 0 of 40 at 2 yr	Berlin, Germany; 40 patients; 26 male, 14 female; age 12–63 yr; previous unsuccessful conservative treatment (time period not stated) Only small “non-contained” disc herniations included	Experimental: percutaneous endoscopic discectomy; control: microdiscectomy	Patient rating; surgeon rating; 2nd procedure required at 2 yr		B
Muralikuttan (1992) ¹⁵	Computer-generated randomization list; blinding: nil; lost to follow-up: 6 of 92 at 1 yr	Belfast, UK; 92 patients; 55 male, 37 female; age 19–60 yr; nerve root pain with/without back pain; failed conservative treatment (minimum 4 wk, including 2-wk bed rest)	Experimental: chymopapain (4000 U); control: discectomy	2nd procedure required; cost analysis at 1 yr		B
Paul (2000) ³⁵	Quasi-randomization by alternation; single blind; lost to follow-up: 0 of 59 at 6 wk	Berlin, Germany; 59 patients; 32 male, 27 female; age mean 53 yr; lumbar disc prolapse with or without stenosis	Experimental: diode laser (940 nm); control: Nd-YAG laser (1964 nm)	Pain score VAS; repeat surgery at 6 wk		C
Revel (1993) ³¹	Permuted block randomization; blinding: nil; lost to follow-up: 2 of 141 at 6 mo	Paris, France; 141 patients; 94 male, 47 female; age 21–65 yr; unsuccessful conservative treatment (minimum 30 days); proven disc herniation at one vertebral level	Experimental: automated percutaneous discectomy; control: chemonucleolysis	Patient rating; 2nd procedure required at 6 mo		B

(Continued)

Table 1. Continued

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation Concealment
Richter (2001) ⁵⁷	Randomization: list; double blind; lost to follow-up: 37 of 398	Ulm, Germany; 398 patients; 221 male, 136 female; mean age 43 yr; unilateral single-level disc prolapse	Experimental: Adcon-L gel; control: no anti-adhesion gel	Patient rating (Hannover score); radicular pain rating; 2nd procedure required at 6 mo		D
Schwetschenau (1976) ³⁸	Randomization method not stated; blinding: double; lost to follow-up: 0 of 66 at 1 yr	Washington, DC; 66 patients; 44 male, 22 female; age 32–40 yr; 1 or more clinical signs of herniated lumbar disc positive myelogram; failed conservative treatment (including at least 3-wk bed rest)	Experimental: chymopapain 20 mg; control: sodium iothalamate (20 mg)	Surgeon rating; 2nd procedure required (laminectomy) at 1 yr		A
Steffen (1996) ³⁶	Randomization method not stated; blinding: independent observer; lost to follow-up: 0 of 69	Bochum, Germany; 69 patients; sex and age not specified	Experimental: laser discectomy; Holmium:YAG; control: chymopapain 4000 IU	Secondary surgery; clinician rating independent at 1 yr		B
Thome (2005) ³⁰	Randomized from a concealed computer-generated list; blinding: nil; lost to follow-up: 11 of 84	Mannheim, Germany; 84 patients; 47 male, 37 female; age 18–60 yr	Experimental: disc sequestrectomy; control: microdiscectomy	Patient satisfaction index; Prolo scale; SF-36- at 1 yr; VAS low back pain and sciatica; repeat surgery	Intraspinal (not extraforaminal) herniations	D
Tullberg (1993) ²⁵	Randomization method not stated; blinding: nil; lost to follow-up: 0 of 60 at 1 yr	Stockholm, Sweden; 60 patients; 39 male, 21 female; age 17–64 yr; single lumbar disc herniation; failed conservative treatment (minimum 2 mo)	Experimental: microdiscectomy control: standard discectomy	Surgeon rating; leg pain score; back pain score; repeat surgery required at 1 yr	Radiographic changes reported in separate publication (Tullberg, 1993)	B
van Alphen (1989) ⁴⁵	Quasi-randomization by alternation; blinding: nil; lost to follow-up: 1 of 151 at 1 yr	Amsterdam, The Netherlands; 151 patients; 99 male, 52 female; age 18–45 yr; proven disc herniation (myelography); failed conservative treatment (including 2-wk minimum bed rest)	Experimental: chemonucleolysis; control: discectomy	Patient rating; surgeon rating; 2nd procedure required at 1 yr		B
Weber (1983) ²¹	Envelope randomization; blinding: nil; lost to follow-up: 5 of 126 at 1 yr	Oslo, Norway; 126 patients; 68 male, 58 female; age 25–55 yr; 5th lumbar +/- or 1st sacral root lesion; failed conservative treatment (minimum 2 wk)	Experimental: discectomy (standard); control: conservative treatment	Independent observer rating; cost analysis reported by Malter <i>et al</i> , 1996 at 1, 4, and 10 yr		A
Weinstein (2006) ²²	Computer-generated random assignment from blocks	Multicenter, US (13 centers); 501 patients; mean age 42 yr; radicular pain with positive nerve-root tensions; signs and imaging	Experimental: discectomy (standard); control: usual care with active physical therapy	SF-36 Oswestry disability index; patient rating; work status		A
Yu (2001) ⁵¹	Randomization method unknown; blinding: double; lost to follow-up: 0 of 156	Chongqing, China; 156 patients; 84 male, 72 female; age 18–67 yr; PLID at L4–L5 or L5–S1	Experimental: collagenase intraprotrusion; control: collagenase intradisc	Success; sciatica not improved at 3 mo		B

crossed-over, although there was an intention-to-treat analysis. Both patient and observer ratings showed that discectomy was significantly better than “conservative therapy” at 1 year, but there were no significant differences in outcomes at 4 and 10 years. Regardless of treatment, impaired motor function had a good prognosis, whereas sensory deficits remained in almost one half of the patients. Malter *et al*¹⁷ reanalyzed Weber’s data and

suggested that discectomy was highly cost-effective, at approximately \$29,000 per QALY gained.

In November 2006, the multicenter U.S. Spine Patient Outcomes Research Trial was published.²² This trial compared standard open discectomy with nonoperative treatment individualized to the patient. Primary outcomes were changes from baseline in the 36-item Short-Form bodily pain and physical function scales and mod-

ified Oswestry Disability Index. The major limitation of the trial was lack of adherence to assigned treatment and the amount of crossover: only 50% of patients assigned to surgery actually received surgery and 30% of those assigned to nonoperative treatment received surgery, within 3 months of enrolment. Both surgically and conservatively treated groups improved substantially on all outcomes over 2 years of follow-up. Intention-to-treat analyses showed that the results tended to favor surgery, but the treatment effects on the primary outcomes were small and not statistically significant. In contrast, as-treated analysis based on treatment received showed strong, statistically significant advantages for surgery on all outcomes at all follow-up times. The amount of crossover makes it likely that the intention-to-treat analysis underestimates the true effect of surgery, but the resulting confounding also makes it impossible to draw any firm conclusions about the efficacy of surgery. Greenfield *et al*²⁰ also compared microdiscectomy with a low-tech physical therapy regimen and educational approach. Although at 12 and 18 months there were statistically significant differences in pain and disability favoring the surgical group, by 24 months this was no longer the case. It should be noted that the patients studied had all presented with low back pain and sciatica and were selected to include those with a small or moderate disc prolapse only.

Butterman²³ compared results following microdiscectomy with those after an epidural steroid injection. Although the authors considered that the control arm was microdiscectomy, it is probably more useful to consider this as the intervention. Patients undergoing discectomy had the most rapid decrease in their symptoms. Twenty-seven of 50 patients receiving a steroid injection had a subsequent microdiscectomy. Outcomes in this crossover group did not appear to have been adversely affected by the delay in surgery. The patients who had a successful epidural steroid injection were twice as likely to have an extruded or sequestered disc as those in whom the injection failed. Very limited data are available from a trial comparing microdiscectomy plus isometric muscle training with plain muscle training²⁴ and this trial is labeled “ongoing.”

Nine of the 42 trials were of different forms or techniques of surgical discectomy. Three trials compared microdiscectomy^{25–27} and one microendoscopic discectomy²⁸ with standard discectomy. Use of the microscope lengthened the operative procedure but did not appear to make any significant difference to perioperative bleeding or other complications, length of inpatient stay, or the formation of scar tissue. Clinical outcome data were not comparable and could not be pooled. The place for microendoscopic discectomy²⁸ is uncertain as the number of patients studied (22) was too small to draw any clear conclusions. Data from a further trial by Hermantin *et al*²⁹ and from a now excluded trial¹² suggest that video arthroscopy may be worth further study. One trial³⁰ compared early outcomes and recurrence rates after se-

questrectomy and microdiscectomy. There was a trend toward better outcome and a lesser rate of secondary surgery after sequestrectomy alone than after removal of the herniated material and resection of disc tissue from the intervertebral space.

Two trials^{31,32} compared automated percutaneous discectomy (APD) with chymopapain and 2 compared it with microdiscectomy.^{16,33} Results from these trials suggest that APD produces inferior results to either more established procedure. However, we do note that Onik *et al*,⁴ the original proponent of APD, suggested that the therapy was only suitable for small-sized herniations, strictly localized in front of the intervertebral space and without a tear of the posterior longitudinal ligament. Ideally, the disc herniation should not occupy more than 30% of the spinal canal. This figure was clearly exceeded in the Revel *et al* series³¹ in which the disc herniation size was 25% to 50% in 59% of the APD and 63% of the chemonucleolysis patients. A fifth trial compared percutaneous endoscopic discectomy (cannula inserted into the central disc) with microdiscectomy.³⁴ This trial showed comparable clinical outcomes after the 2 procedures but the study group of 40 patients was small. No trial looked specifically at transforaminal endoscopic discectomy or foraminotomy.

There are now 2 included trials of laser discectomy. In their QRCT, Hellinger³⁵ compared the effects of a Nd-YAG-laser (1064 nm) with that of a diode laser (940 nm). Both produced only slight vaporization but excellent shrinkage of disc tissue. However, no comparative outcome results were published. Steffen *et al*³⁶ published 3 abstracts detailing results from a comparative study of chemonucleolysis and laser discectomy. The limited results favored chemonucleolysis. In a third trial, no significant difference was demonstrated between outcomes following laser use and that obtained after an epidural injection,³⁷ but the trial was aborted before its conclusion and therefore “excluded.” Statistical pooling was not possible due to the clinical heterogeneity of the trials and there were insufficient data to calculate effect size.

Chemonucleolysis

Seventeen of the 42 trials were of some form of chemonucleolysis. Use of chymopapain is now rare, so this may turn out to be a final summary of the historical evidence on chemonucleolysis.

Five trials^{38–42} compared the efficacy of chemonucleolysis using chymopapain *versus* placebo. These trials had the highest quality scores in this review, with generally adequate randomization, double-blinding, and independent outcome assessment. In all the trials, chymopapain was injected by standard technique. The combined results from the 5 trials compared data from 446 patients with an average follow up of 97%. Meta-analysis clearly showed that chymopapain was more effective than placebo whether rated by the patients (random effects model OR = 0.24; 95% CI, 0.12–0.49; Figure 1), or rated by surgeons conducting the study or by an independent ob-

Review: Surgical interventions for lumbar disc prolapse
 Comparison: 01 CHYMOPAPAIN V. PLACEBO
 Outcome: 14 No success at 3-12 mths - independent observer rated

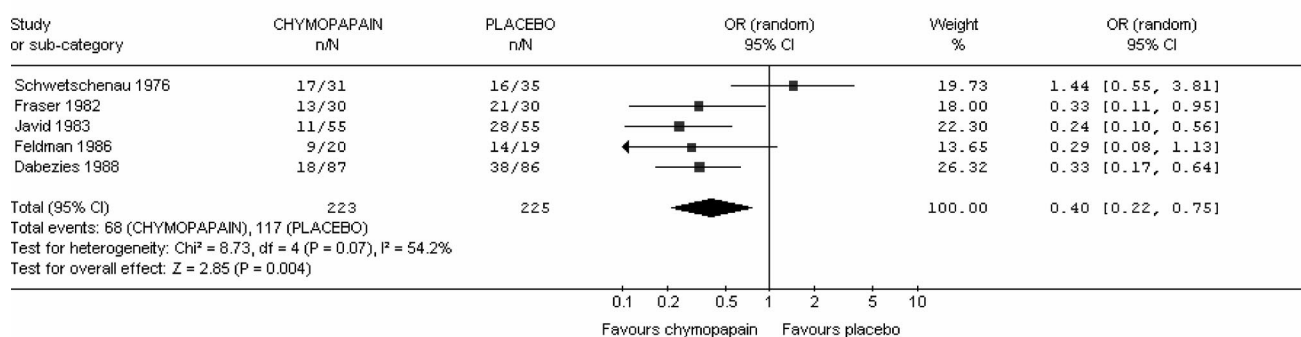


Figure 1. Failure rated independently of chymopapain and placebo injection.

server (random OR = 0.40; 95% CI, 0.21–0.75). Fewer patients after chymopapain injection proceeded to open discectomy (random OR = 0.41; 95% CI, 0.25–0.68).

Another 5 trials,^{14,15,43–45} one of which was a QRCT,⁴⁵ compared chemonucleolysis using chymopapain and surgical discectomy. In each instance, a set dose of chymopapain was injected by standard technique and compared with standard discectomy. In all the trials, there was a poor description of the method of randomization, and the nature of these studies precluded blinding of the patients. The combined results from the 5 trials compared data from 680 patients with an average follow-up of 97%. Note that the test for heterogeneity was significant in this group of trials. Nevertheless, there is strong clinical rationale for pooling this group of trials and in view of the clinical importance of the issue these results are presented as the best available information at present, with the qualification that there may be statistical weaknesses to the results. All of the analyses showed consistently poorer results with chemonucleolysis, although this did not reach statistical significance in the random effects model. Two trials^{43,45} showed a worse result at 1 year as rated by the patients (random OR = 0.61; 95% CI, 0.30–1.24). Three trials^{14,44,45} showed a poorer result at 1 year as rated by the surgeon (fixed OR = 0.52; 95% CI, 0.35–0.78, Figure 2a; random OR = 0.37; 95% CI, 0.13–1.05, Figure 2b). About 30% of patients with chemonucleolysis had further disc sur-

gery within 2 years, and meta-analysis showed that a second procedure was more likely after chemonucleolysis (random OR = 0.07; 95% CI, 0.02–0.18, Figure 3). However, chemonucleolysis is a less invasive procedure, which may be regarded as an intermediate stage between conservative and surgical treatment, and surgery following failed chemonucleolysis is not strictly comparable to repeat surgery after failed discectomy. There was some suggestion that the results of discectomy after failed chemonucleolysis are poorer than primary discectomy, but there were insufficient data to allow meta-analysis and in any event, the patient subgroups so derived were unlikely to be comparable. The main meta-analysis shows that the final outcome of patients treated by chemonucleolysis, including the effects of further surgery if chemonucleolysis failed, remained poorer than those treated by primary discectomy.

No statistically significant differences were demonstrated between low-dose and standard-dose chymopapain,⁴⁶ between chymopapain and collagenase,⁴⁷ or between chymopapain and steroid injection.^{48,49} It should be noted that, although one trial suggested that collagenase was more effective than placebo, that was a small study and there was 40% code break by 8 weeks.⁵⁰ A single study⁵¹ shows a marginally better effect of collagenase if injected into a disc protrusion rather than into the main disc itself.

Review: Surgical interventions for lumbar disc prolapse
 Comparison: 02 DISCECTOMY V. CHYMOPAPAIN
 Outcome: 02 Poor outcome obtained at 1 yr - surgeon rated

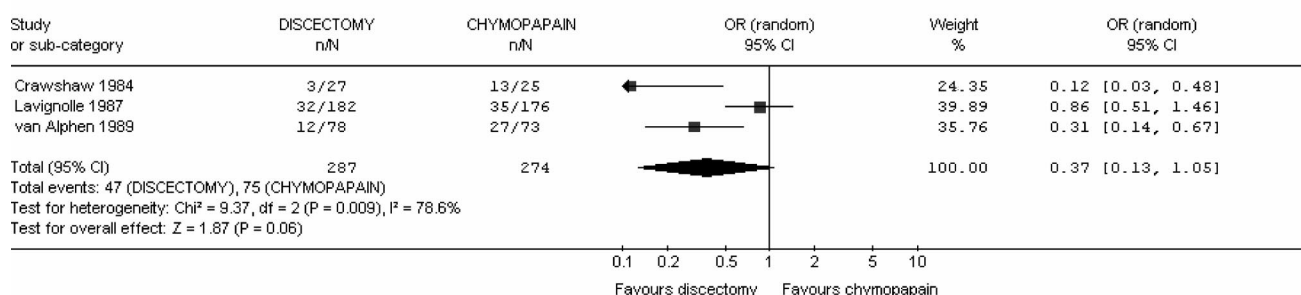


Figure 2. Poor surgeon rating after discectomy and chymopapain.

Review: Surgical interventions for lumbar disc prolapse
 Comparison: 02 DISCECTOMY V. CHYMOPAPAIN
 Outcome: 05 2nd procedure needed within 1 yr

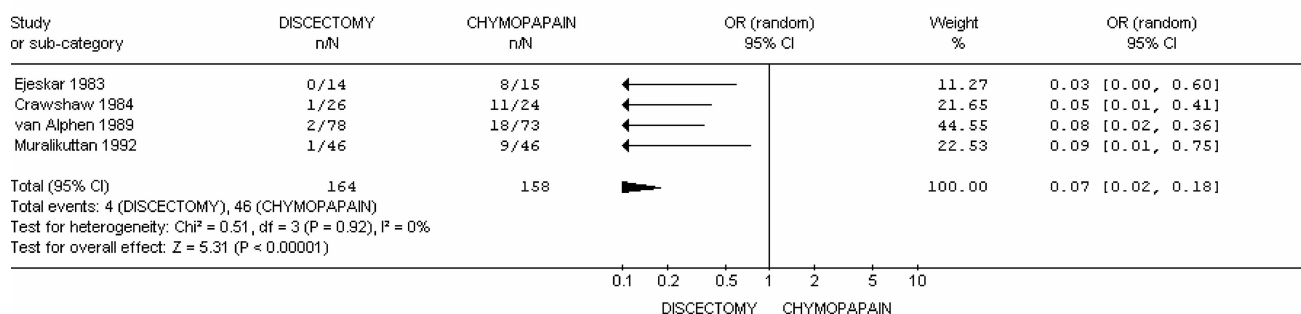


Figure 3. Requirement for a second procedure within 1 year of discectomy and chypopapain injection.

Barrier Membranes

Eight trials considered the effect of different types of interposition membrane on the formation of intraspinal scarring following discectomy, as assessed by magnetic resonance imaging or enhanced computed tomography. Three of the trials^{52–54} failed to show any improvement in clinical outcomes following use of fat or gelfoam, although a lesser number of painful episodes 1 year after surgery was recorded in a fourth trial.⁵⁵ There are 3 trials of ADCON-L an anti-adhesion gel derived from porcine collagen and dextran sulfate. Results from the European^{56,57} and U.S.¹⁸ multicenter studies show conflicting results. Twelve-month results are reported from a pilot study of Oxiplex/SP gel.⁵⁸ Although there is a trend suggesting that treatment diminishes leg pain severity and lower limb weakness, the study had very low power and the results reported are not significant. A polylactic acid membrane was shown to prevent epidural scar adhesion without effect on outcome.⁵⁹

Discussion

The results from 40 RCTs and 2 QRCTs of surgical interventions for lumbar disc prolapse are now presented, including 17 new trials since the first issue of this review. Although, as we have pointed out, there were many weaknesses of trial design and data have to be interpreted with caution, it is possible to draw a number of provisional conclusions.

The trial by Weber²¹ is widely quoted as a direct comparison of discectomy and conservative treatment, and as showing a temporary benefit in clinical outcomes at 1 year, but no difference on longer-term follow-up at 4 and 10 years. We think that this is an inaccurate interpretation of the results (see also Bessette *et al*⁶⁰ for a critique of this trial). Weber²¹ actually reported on a subgroup of patients with uncertain indications for surgery: of a total series of 280 patients, 67 were considered to have definite indications for surgery, 87 patients improved with conservative management, and only the intermediate 126 were randomized in the trial. The intervention consisted of primary discectomy compared with initial conservative management followed by discectomy as soon as

clinically considered necessary if the patient failed to improve. The trial did show clearly that discectomy produced better clinical outcomes at 1 year, particularly for relief of sciatica. What it also showed is that, if the clinical indications are uncertain, postponing surgery to further assess clinical progress may delay recovery but does not produce long-term harm. There are now 3 further trials comparing discectomy with conservative treatment,^{20,22,23} the conclusions of which appear broadly comparable to those from Weber.

At present, the best scientific evidence on the effectiveness of discectomy still comes from chemonucleolysis. There is strong evidence that discectomy is more effective than chemonucleolysis and that chemonucleolysis is more effective than placebo: that is, discectomy is more effective than placebo. This is entirely consistent with systematic reviews^{13,61} of non-RCT series of discectomy and many clinical series which have shown consistently that 65% to 90% of patients get good or excellent outcomes, particularly for the relief of sciatica and for at least 6 to 24 months, compared with 36% of conservatively treated patients.¹³ It is not possible to draw any conclusions about indications for surgery from the present review of RCTs, but these other reviews^{13,61} provide evidence on the need for careful selection of patients. All of this evidence confirms clinical experience and teaching that the primary benefit of discectomy is to provide more rapid relief of sciatica in those patients who have failed to resolve with conservative management, even if there is no clear evidence that surgery alters the long-term natural history or prognosis of the underlying disc disease. The medium-term clinical outcomes have been sufficiently consistent for discectomy to survive the test of time in widespread clinical practice for more than 60 years.

This review also provides evidence on a number of technical questions about discectomy. There is moderate evidence from 3 trials that the clinical outcomes of microdiscectomy are comparable to those of standard discectomy. In principle, the microscope provides better illumination and facilitates teaching. These trials suggest that use of the microscope lengthens the operative procedure; but despite previous concerns, they did not show

any significant difference in perioperative bleeding, length of inpatient stay, or the formation of scar tissue. It is probable that some form of interposition membrane may reduce scarring after discectomy, although there is no clear evidence on clinical outcomes.

Enthusiasm for chemonucleolysis with chymopapain has waxed and waned. After 40 years, there remains good evidence on its effectiveness: 5 generally high-quality trials show that chemonucleolysis produces better clinical outcomes than placebo, and one trial showed that these outcomes are maintained for ten years. Conversely, however, there is strong evidence that chemonucleolysis does not produce as good clinical outcomes as discectomy, even if that must be balanced against a lower overall complication rate.⁶² Moreover, a significant proportion of patients progress to surgery anyway after failed chemonucleolysis and their final outcome may not be quite as good. Rationally, chemonucleolysis is a minimally invasive procedure, which might be considered as an intermediate stage between conservative management and open surgical intervention, and could save about 70% of patients from requiring open surgery. It is then a matter of debate about the relative balance of possibly avoiding surgery, relative risks and complication rates, clinical outcomes over the next year or so, and the potential impact on the lifetime natural history of disc disease. In current practice, that balance of advantages and disadvantages has put chemonucleolysis out of favor.

The place for other forms of discectomy is unresolved. Trials of automated percutaneous discectomy and laser discectomy suggest that clinical outcomes following treatment are at best fair and certainly worse than after microdiscectomy, although the importance of patient selection (see Results) is acknowledged. There are no RCTs examining intradiscal electrotherapy or coblation as a treatment for disc prolapse, nor as yet any comparing transforaminal endoscopic (arthroscopic) discectomy advocated for small subligamentous prolapse.

Although a few trials report the number of patients who return to work after treatment, there are insufficient data to draw any conclusions about the effectiveness of any of these surgical treatments on capacity for work. Readers are referred to older, non-RCT reviews and discussions by Taylor⁶³ and Scheer *et al.*⁶⁴

■ Conclusion

Implications for Practice

Epidemiologic and clinical studies show that most lumbar disc prolapses resolve naturally with conservative management and the passage of time and without surgery.

There is considerable evidence that surgical discectomy provides effective clinical relief for carefully selected patients with sciatica due to lumbar disc prolapse that fails to resolve with conservative management. It provides faster relief from the acute attack of sciatica, although any positive or negative effects on the long-term

natural history of the underlying disc disease are unclear. There is still a lack of scientific evidence on the optimal timing of surgery.

The choice of microdiscectomy or standard discectomy at present probably depends more on the training and expertise of the surgeon and the resources available than on scientific evidence of efficacy. However, it is worth noting that some form of magnification is now used almost universally in major spinal surgical units to facilitate vision.

At present, unless or until better scientific evidence is available, automated percutaneous discectomy, coblation therapy, and laser discectomy should be regarded as research techniques.

Implications for Research

The quality of surgical RCTs still needs to be improved, particularly on the issues of sufficient power, adequate randomization, blinding, duration of follow-up, and better clinical outcome measures. There are major gaps in our knowledge on the costs and cost-effectiveness of all forms of surgical treatment of lumbar disc prolapse. Authors of future surgical RCTs should seek expert methodologic advice at the planning stage.

There is still a need for more and better evidence on 1) the optimal selection and timing of surgical treatment in the overall and long-term management strategy for disc disease, 2) the outcomes of discectomy *versus* conservative management, and 3) the relative clinical outcomes, morbidity, costs and cost-effectiveness of microdiscectomy *versus* standard discectomy. High-quality RCTs are required to determine if there is any role for automated percutaneous discectomy or laser discectomy. There is a major need for long-term studies into the effects of surgery on the lifetime natural history of disc disease and on occupational outcomes.

This Cochrane review should continue to be maintained and updated as further RCTs become available. The authors will be pleased to receive information about any new RCTs of surgical treatment of lumbar disc prolapse.

■ Key Points

- Forty randomized and 2 quasi-randomized controlled trials are presented in this updated Cochrane review.
- Seventeen trials are new since 1998.
- Discectomy for patients with sciatica from PLID provides faster relief from the acute attack than nonoperative treatment.
- Microdiscectomy gives broadly comparable results to open discectomy.
- The evidence on other minimally invasive techniques remains unclear (with the exception of chymopapain, which is no longer widely available).

Acknowledgments

The authors thank Dr. M. Szpalski and the late Professor A. Nachemson who provided much assistance in literature searching and retrieval over the years and to Ms. Victoria Pennick and the staff of the Cochrane Back Review Group for their editorial work.

References

- Carlisle E, Luna M, Stou PM, et al. Percent spinal canal compromise on MRI utilized for predicting the need for surgical treatment in single-level lumbar intervertebral disc herniation. *Spine J* 2005;5:608–14.
- Carragee EJ, Han MY, Suen PW, et al. Clinical outcomes after lumbar discectomy for sciatica: the effects of fragment type and anular competence. *J Bone Joint Surg Am* 2003;85:102–8.
- Smith L. Enzyme dissolution of nucleus pulposus in humans. *JAMA* 1964; 187:137–40.
- Onik G, Mooney V, Maroon JC, et al. Automated percutaneous discectomy: a prospective multi-institutional study. *Neurosurgery* 1990;2:228–33.
- Kahanovich N, Viola K, McCulloch JA. Limited surgical discectomy and microdiscectomy: a clinical comparison. *Spine* 1989;14:79–81.
- Kambin P, Vaccaro A. Arthroscopic microdiscectomy. 2003;3(suppl 1): 60–4.
- Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions* [4.2.4] (updated March 2005). www.cochrane.org/resources/handbook/hbook.htm (accessed March 31, 2005).
- Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408–12.
- Deyo RA, Battie M, Beurskens AJHM, et al. Outcome measures for low back pain research: a proposal for standardized use. *Spine* 1998;23:2003–13.
- North RB, Kidd DH, Piantadosi S. Spinal cord stimulation versus reoperation for failed back surgery syndrome: a prospective, randomized study design. *Acta Neurochir* 1995;64:106–8.
- Petrie JL, Ross JS. Use of ADCON-L to inhibit postoperative peridural fibrosis and related symptoms following lumbar disc surgery: a preliminary report. *Eur Spine J* 1996;5(suppl):10–7.
- Chung J-Y. A prospective randomized study of arthroscopic and microscopic discectomy in protruded type lumbar disc herniation. In: *Proceedings of ISSLS Meeting*, 1999, Hawaii.
- Hoffman RM, Wheeler KJ, Deyo RA. Surgery for herniated lumbar discs: a literature synthesis. *J Gen Int Med* 1993;8:487–96.
- Lavignolle B, Vital JM, Baulny D, et al. Etudes comparees de la chirurgie et de la chimionucleolyse dans le traitement de la sciatique par hernie discale [Comparative study of surgery and chemonucleolysis in the treatment of sciatica caused by a herniated disk]. *Acta Orthop Belg* 1987;53:244–9.
- Muralikuttan KP, Hamilton A, Kernohan WG, et al. A prospective randomized trial of chemonucleolysis and conventional disc surgery in single level lumbar disc herniation. *Spine* 1992;17:381–7.
- Chatterjee S, Foy PM, Findlay GF. Report of a controlled clinical trial comparing automated percutaneous lumbar discectomy and microdiscectomy in the treatment of contained lumbar disc herniation. *Spine* 1995;20:734–8.
- Malter AD, Larson EB, Urban N, et al. Cost-effectiveness of lumbar discectomy for the treatment of herniated inter-vertebral disc. *Spine* 1996;21: 1048–55.
- Geisler FH. Prevention of peridural fibrosis: current methodologies. *Neurol Res* 1999;21(suppl 1):9–22.
- Goosens M, Evers S. Economic evaluation of back pain interventions. In: Nachemson A, Jonsson E, eds. *SBU Report on Back Pain*. Stockholm: Swedish Council on Technology Assessment in Health Care: Swedish Council on Technology Assessment in Health Care; 1998.
- Greenfield K, Nelson RJ, Findlay GD, et al. Microdiscectomy and conservative treatment for lumbar disc herniation with back pain and sciatica: a randomized clinical trial. In: *Proceedings of the International Society for the Study of the Lumbar Spine*, 2003:245.
- Weber H. Lumbar disc herniation: a controlled, prospective study with ten years of observation. *Spine* 1983;8:131–40.
- Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical vs nonoperative treatment for lumbar disk herniation. The Spine Patient Outcomes Research Trial (SPORT): a randomized trial. *JAMA* 2006;296:2451–9.
- Butterman GR. Treatment of lumbar disc herniation: epidural steroid injection compared with discectomy. *J Bone Joint Surg Am* 2004;86:670–9.
- Osterman H, Seitsalo S, Malmivaara A. Six-year outcomes of lumbar microdiscectomy: results of a randomized controlled trial. *Proceedings of the International Society for the Study of the Lumbar Spine*, 2005:18.
- Tullberg T, Isacson J, Weidenhielm L. Does microscopic removal of lumbar disc herniation lead to better results than the standard procedure? Results of a one-year randomized study. *Spine* 1993;18:24–7.
- Lagarrigue J, Chaynes P. Etude comparative de la chirurgie discale avec et sans microscope [Comparative study of disk surgery with or without microscopy. A prospective study of 80 cases]. *Neurochirurgie* 1994;40:116–20.
- Henrikson L, Schmidt V, Eskesen V, et al. A controlled study of microsurgical versus standard lumbar discectomy. *Br J Neurosurg* 1996;10:289–93.
- Huang T-J, Hsu RW-W, Li Y-Y. Less systemic cytokine response in patients following microscopic versus open lumbar discectomy. *J Orthop Res* 2005;23:406–11.
- Hermanting FU, Peters T, Quartararo L, et al. A prospective, randomized study comparing the results of open discectomy with those of video-assisted arthroscopic microdiscectomy. *J Bone Joint Surg* 1999;81:958–65.
- Thome C, Barth M, Scharf J, et al. Outcome after lumbar sequestrectomy compared with microdiscectomy: a prospective randomized study. *J Neurosurg Spine* 2005;2:271–8.
- Revel M, Payan C, Vallee C, et al. Automated percutaneous lumbar discectomy versus chemonucleolysis in the treatment of sciatica: a randomized multicenter trial. *Spine* 1993;18:1–7.
- Krugluger J, Knahr K. Chemonucleolysis and automated percutaneous discectomy: a prospective randomized comparison. *Int Orthop* 2000;24:167–9.
- Haines SJ, Jordan N, Boen JR, et al. Discectomy strategies for lumbar disc herniation: results of the LAPDOG trial. *J Clin Neurosci* 2002;9:411–7.
- Mayer HM, Brock M. Percutaneous endoscopic discectomy: surgical technique and preliminary results compared to microsurgical discectomy. *J Neurosurg* 1993;78:216–25.
- Hellinger PM. Nd-YAG (1064nm) versus diode (940nm) PLDN: a prospective randomised blinded study. In: Brock M, Schwarz W, Wille C, eds. *Proceedings of the First Interdisciplinary World Congress on Spinal Surgery and Related Disciplines*. 2000:555–8.
- Steffen R, Luetke A, Wittenberg RH, et al. A prospective comparative study of chemonucleolysis and laser discectomy. *Orthop Trans*. 1996;20:388.
- Livesey JP, Sundaram S, Foster L, et al. Laser discectomy versus lumbar epidural steroid injection: a randomised comparative study of two treatments for sciatica. *J Bone Joint Surg Br* 2000;82:74.
- Schwetschenau R, Ramirez A, Johnston J, et al. Double-blind evaluation of intradiscal chymopapain for herniated lumbar discs: early results. *J Neurosurg* 1976;45:622–7.
- Fraser RD. Chymopapain for the treatment of intervertebral disc herniation: a preliminary report of a double-blind study. *Spine* 1982;7:608–12.
- Javid MJ, Nordby EJ, Ford LT, et al. Safety and efficacy of chymopapain (chymodiactin) in herniated nucleus pulposus with sciatica. *JAMA* 1983; 249:2489–94.
- Feldman J, Menkes CJ, Pallardy G, et al. Etude en double-aveugle du traitement de la lombosciatique discale par chimionucleolyse [Double-blind study of the treatment of disc lombosciatica by chemonucleolysis]. *Rev Rhum Mal Osteoartic* 1986;53:147–52.
- Dabezies EJ, Langford K, Morris J, et al. Safety and efficacy of chymopapain (Discase) in the treatment of sciatica due to a herniated nucleus pulposus. Results of a randomized, double-blind study. *Spine* 1988;13:561–5.
- Ejeskar A, Nachemson A, Herbergs P, et al. Surgery versus chemonucleolysis for herniated lumbar discs: a prospective study with random assignment. *Clin Orthop* 1983;174:236–42.
- Crawshaw C, Frazer AM, Merriam WF, et al. A comparison of surgery and chemonucleolysis in the treatment of sciatica: a prospective randomized trial. *Spine* 1984;9:195–8.
- van Alphen HA, Braakman R, Bezemer PD, et al. Chemonucleolysis versus discectomy: a randomized multicenter trial. *J Neurosurg* 1989;70:869–75.
- Benoist M, Bonneville JF, Lassale B, et al. A randomized, double-blind study to compare low-dose with standard-dose chymopapain in the treatment of herniated lumbar intervertebral discs. *Spine* 1993;18:28–34.
- Hedtman A, Fett H, Steffen R, et al. Chemonucleolyse mit Chymopapain und Kollagenase. 3-Jahres-Ergebnisse einer prospektiv-randomisierten Studie [Chemonucleolysis using chymopapain and collagenase. 3-year results of a prospective randomized study]. *Z Orthop Ihre Grenzgeb* 1992; 130:36–44.
- Bourgeois P, Benoist M, Palazzo E, et al. Etude en double aveugle randomisee multicentrique de l'hexacetonide de triamcinolone versus chymopapaine dans le traitement de la lombosciatique discale. Premiers resultats a six mois [Multicenter randomized double-blind study of triamcinolone hexacetonide versus chymopapain in the treatment of disk lombosciatica. Initial results at 6 months]. *Rev Rhum Mal Osteoartic* 1988;55:767–9.
- Bontoux D, Alcalay M, Debiais F, et al. Traitement des hernies discales lombaires par injection intradiscale de chymopapaine ou d'hexacetonide de triamcinolone. Etude comparee de 80 cases [Treatment of lumbar disk hernia

- by intra-disk injection of chymopapain or triamcinolone hexacetonide: comparative study of 80 cases]. *Rev Rhum Mal Osteoartic* 1990;57:327-31.
50. Bromley JW, Varma AO, Santoro AJ, et al. Double-blind evaluation of collagenase injections for herniated lumbar discs. *Spine* 1984;9:486-8.
 51. Yu L, Wu N, Zhang K. An investigation on the treatment of intraprotrusion or intradisk injection with collagenase for lumbar disc herniation. *Chin J Clin Rehabil* 2002;6:598-9.
 52. MacKay MA, Fischgrund JS, Herkowitz HN, et al. The effect of interposition membrane on the outcome of lumbar laminectomy and discectomy. *Spine* 1995;20:1793-6.
 53. Jensen TT, Asmussen K, Berg-Hansen E-MB, et al. First-time operation for lumbar disc herniation with or without free fat transplantation: prospective triple-blind randomized study with reference to clinical factors and enhanced computed tomographic scan 1 year after operation. *Spine* 1996;21:1072-6.
 54. Bernsmann K, Kramer J, Ziozios I, et al. Lumbar micro disc surgery with and without autologous fat graft. *Arch Orthop Trauma Surg* 2001;121:476-80.
 55. Gambardella G, Gervasio O, Zaccone C, et al. Prevention of recurrent radicular pain after lumbar disc surgery: a prospective study. *Acta Neurochir* 2005;92:151-4.
 56. De Tribolet N, Porchet F, Lutz TW, et al. Clinical assessment of a novel antiadhesion barrier gel: prospective, randomised multicenter clinical trial of ADCON-L to inhibit postoperative peridural fibrosis and related symptoms after lumbar discectomy. *Am J Orthop* 1998;111-20.
 57. Richter H, Kast E, Tomczak R, et al. Results of applying ADCON-L gel after lumbar discectomy: the German ADCON-L study. *J Neurosurg* 2001;95:179-89.
 58. Kim KD, Wang JC, Robertson DP, et al. Reduction in leg pain and lower-extremity weakness with Oxiplex/SP Gel for 1 year after laminectomy, laminotomy and discectomy. *Neurosurg Focus* 2004;17:1-6.
 59. Huang J-J, Song Y-M, Liu L-M. Clinical study of prevention of epidural scar and adhesion with polylactic acid membrane. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2004;18:21-4.
 60. Bessette L, Liang MH, Lew RA, et al. Classics in spine surgery revisited. *Spine* 1996;21:259-63.
 61. Stevens CD, Dubois RW, Larequi-Lauber T, et al. Efficacy of lumbar discectomy and percutaneous treatments for lumbar disc herniation. *Soz-Pravedtivmed* 1997;42:367-79.
 62. Bouillet R. Complications de la nucleolyse discale par la chymopapaine. *Acta Orthop Belg* 1987;53:250-60.
 63. Taylor ME. Return to work following back surgery: a review. *Am J Ind Med* 1989;16:79-88.
 64. Scheer SJ, Radack KL, O'Brien DR. Randomised controlled trials in industrial low back pain relating to return to work: Part 2. Discogenic low back pain. *Arch Phys Med Rehabil* 1996;77:1189-97.