

Maurits W. van Tulder
Bart Koes
Seppo Seitsalo
Antti Malmivaara

Outcome of invasive treatment modalities on back pain and sciatica: an evidence-based review

Received: 19 October 2005
Accepted: 25 October 2005
Published online: 1 December 2005
© Springer-Verlag 2005

A. Malmivaara
Finnish Office for Health Care Technology
Assessment, P.O. Box 220, FIN-00531
Stakes, Finland

M. W. van Tulder (✉)
Institute for Research in Extramural
Medicine (EMGO), VU University Medical
Center, van der Boechorststraat 7, 1081 BT
Amsterdam, The Netherlands
E-mail: mw.vantulder@vumc.nl
Tel.: +31-20-4448178
Fax: +31-20-4446775

M. W. van Tulder
Institute for Health Sciences, Faculty of
Earth & Life Sciences, Free University,
de Boelelaan 1085, 1081 HV Amsterdam,
The Netherlands

B. Koes
Department of General Practice, Erasmus
University Medical Center Rotterdam,
P.O. Box 1738, 3000 DR Rotterdam,
The Netherlands

S. Seitsalo
ORTON Orthopaedic Hospital,
Tenholantie 10, 00280 Helsinki, Finland

Abstract Within the framework of evidence-based medicine high-quality randomised trials and systematic reviews are considered a necessary prerequisite for progress in orthopaedics. This paper summarises the currently available evidence on surgical and other invasive procedures for low back pain. Results of systematic reviews conducted within the framework of the Cochrane Back Review Group were used. Data were gathered from the latest Cochrane Database of Systematic Reviews 2005, Issue 2. The Cochrane reviews were updated using the evidence summary on surgery and other invasive procedures from the COST B13 European Guidelines for the Management of Acute and Chronic Non-Specific Low Back Pain. Facet

joint, epidural, trigger point and sclerosant injections have not clearly been shown to be effective and can consequently not be recommended. There is no scientific evidence on the effectiveness of spinal stenosis surgery. Surgical discectomy may be considered for selected patients with sciatica due to lumbar disc prolapses that fail to resolve with the conservative management. Cognitive intervention Combined with exercises is recommended for chronic low back pain, and fusion surgery may be considered only in carefully selected patients after active rehabilitation programmes during 2 years time have failed. Demanding surgical fusion techniques are not better than the traditional posterolateral fusion without internal fixation.

Keywords Back pain · Sciatica · Invasive treatment · Surgery · Evidence review

Introduction

Compared to conservative treatments, less evidence is available for surgical and other invasive interventions for low back pain. However, there is an increasing acceptance among the orthopaedic community of the principles of evidence-based medicine. The first randomised controlled trial (RCT) on conservative vs operative treatment of disc prolapse was published by Weber

in 1978 [95]. Since that time, several trials have been published and their need has been generally acknowledged [25]. However, even at present, the effectiveness of some spinal surgical procedures has not been evaluated in RCTs. Also the majority of the trials have compared the various surgical or other invasive procedures, but there are only a few trials that have compared the surgery with the conservative treatment. The trial by Weber is still the only one published on surgery compared with

conservative treatment for disc prolapse [95, 96]. Also, many new technologies are introduced in spine surgery and used in clinical practice without any scientific evidence of the effectiveness.

Within the framework of evidence-based medicine, high-quality randomised trials and systematic reviews are considered a necessary prerequisite for progress in orthopaedics. This paper summarises the currently available evidence on surgical and other invasive procedures for low back pain.

Objectives

To determine the effectiveness of surgery and other invasive procedures for low back pain.

Methods

Results of systematic reviews conducted within the framework of the Cochrane Back Review Group were used [7]. Data were gathered from the latest Cochrane Database of Systematic Reviews 2005, Issue 2. The last amendment of the review on injection therapy for sub-acute and chronic benign low back pain was made in 1996 [70], on surgery for lumbar disc prolapse in March 1997 [36], on radiofrequency denervation in April 2002 [71], on prolotherapy in January 2004 [98], and on surgery for degenerative lumbar spondylosis (including lytic spondylolisthesis) in February 2005 [37]. Surgery for specific pathologies such as tumours, trauma, infection, and myelopathic syndromes were excluded. Surgery for disc prolapse and spinal stenosis, and fusion for chronic low back pain were included.

We updated the Cochrane reviews using the evidence summary on surgery and other invasive procedures from the COST B13 European Guidelines for the Management of Acute and Chronic Non-Specific Low Back Pain (<http://www.backpaineurope.org>). The final search date of these European guidelines was May 2005. If no summary of the European guidelines is provided in the results section, no additional trials were identified.

Results

Injection therapy

Injection with anaesthetics and/or steroids is applied on different locations. Injections into facet joints have been presented as treatment as well as a diagnostic test for the lumbar facet joint syndrome. There are no objective criteria for this syndrome. The clinical diagnosis is made on the presence of localised lumbar pain which may radiate to the posterior aspect of the thigh and be relieved by an injection of corticosteroids and local

anaesthetic. Injections can be given intra-articularly, peri-articularly or periradicularly. In epidural anaesthesia, a solution of local anaesthetic is injected into the epidural space.

Effectiveness for acute low back pain

The Cochrane review excluded one trial that compared trigger point vs placebo for acute low back pain, because this trial was not randomised [33].

Effectiveness for chronic low back pain

Epidural injections vs placebo The Cochrane review included four explanatory trials on the short-term efficacy of epidural injections with corticosteroid plus procaine or saline compared with procaine or saline injections [3, 12, 15, 20]. The pooled analysis showed no significant difference in pain relief after 6 weeks (pooled RR 0.92; 95% CI 0.76–1.11) and 6 months (pooled RR 0.93; 95% CI 0.79–1.09) [33].

The European guidelines identified two additional trials. One reported that the injection of a combination of methylprednisolone and bupivacaine at the affected nerve root had a better short-term effect than the injection of saline on leg pain, straight-leg raising and patient satisfaction in patients with subacute/chronic sciatica [48]. However, these effects were not maintained beyond 4 weeks. The other additional trial showed that epidural perineural (lateral and ventral part of the epidural space) injections with steroids ($N=24$ patients) had a better effect (MacNab criteria: leg pain, back pain, return to work, ability to do sport) than saline injections ($N=25$ patients) in patients with lumbar radicular syndromes after 3 weeks and 3 months [54].

Epidural injections vs other interventions The Cochrane review included six pragmatic trials that reported on short-term pain relief [8, 22, 38, 63, 77, 78]. Four of these six trials showed a non-significant positive effect of corticosteroids compared to other procedures. One study showed a significant difference between morphine–steroid and saline–steroid injections with respect to pain relief within 6 weeks [22]. However, only 65% of the patients reported pain relief which lasted 1 day to 6 weeks, whilst morphine frequently caused adverse side effects. None of the two pragmatic trials reporting on long-term pain relief by epidural injection reported statistically significant differences between the treatment groups [63, 83].

The European guidelines identified five additional trials. One additional study reported that epidural perineural (lateral and ventral part of the epidural space) injections with corticosteroids ($N=40$ patients) had a better effect (MacNab criteria: leg pain, back pain,

return to work, ability to do sport) than conventional epidural injections ($N=47$ patients) in patients with lumbar radicular syndromes [54]. Follow-up was 3 weeks and 3 months. Another additional trial showed no statistically significant differences between CT guided injections of the nerve root ($N=20$ patients) and fluoroscopic guided injections ($N=20$ patients) [61]. In one additional trial ($N=55$ patients) selective nerve root injection with betamethasone and bupivacaine resulted in fewer patients going on to surgery than injection with bupivacaine alone [76]. In one additional trial, patients receiving transforaminal epidural steroid injections had a statistically significant higher success rate of 84% compared with 48% for patients receiving trigger-point injections after an average follow-up period of 1.4 years [90]. Finally, one additional trial found no statistically significant differences in pain intensity between hypertonic saline plus hyaluronidase ($N=17$), hypertonic saline ($N=15$), isotonic saline ($N=17$), isotonic saline plus hyaluronidase ($N=10$), each in combination with corticosteroid and local anaesthetic [42].

Facet joint injections vs placebo One study did not find significant differences in proportions with pain improvement between corticosteroid and saline injections at 1 and 3 months after injection: short-term RR 0.89 (0.65–1.21), and long-term RR 0.90 (0.69–1.17) [14]. At 6 months, the percentage of patients with marked or very marked improvement was significantly higher in the group treated with methylprednisolone (46 vs 15%, $P=0.002$). Despite this latter finding, the authors concluded that the efficacy of facet joint injections was small, because 11 of the 22 patients in the steroid group, who reported substantial improvement at 6 months after injection, reported no benefit at earlier evaluations. Moreover, co-interventions were more frequent in the steroid group.

Another study reported that mean scores for pain relief with methylprednisolone and/or bupivacaine were not superior compared to placebo injections [58, 59]. This study did not report the proportions of patients with pain relief.

Facet joint injections vs other interventions One pragmatic trial found no significant differences between facet joint injections with methylprednisolone and lignocaine compared with facet nerve blocks of the medial articular branch of the posterior primary ramus from L1 to L4 [62]. Short-term RR was 0.81 (0.62–1.06) and long-term RR was 0.91 (0.74–1.12).

Prolotherapy (sclerosant injections) vs placebo The Cochrane review included one trial ($N=110$) [97]. No statistically significant differences were found on pain and disability between fortnightly injections (mean of seven injections) of lumbopelvic ligaments with glucose

(20%) and lignocaine (0.2%), 10–30 ml, and injections with saline (0.9%) after 6, 12 and 24 months.

Prolotherapy (sclerosant injections) vs other interventions The Cochrane review [97] included three trials [23, 52, 72]. Two studies reported statistically significant differences in favour of prolotherapy in the proportion to the participants showing more than 50% reduction in scores from the baseline at 6 months: 88 vs 39% [72] and 77 vs 53% [52]. The third trial did not show any differences in pain and disability after 6 months [23].

Trigger point injections vs placebo The Cochrane review included four trials [18, 35, 41, 87]. Three of these studies indicated that injection therapy with lidocaine was more effective than saline injection [18, 41, 87]. Pooled analysis of the proportions of patients with short-term pain relief did not show a statistically significant difference (RR 0.80; 95% CI 0.40–1.59) [18, 35, 87].

Intradiscal injections vs other interventions The Cochrane review included one small trial ($N=25$) that did not find a statistically significant difference in the short-term pain relief between intradiscal injections of methylprednisolone and bupivacaine in patients with and without sciatica [85]. The European guidelines identified two additional trials. One trial ($N=120$) did not find significant differences in pain and disability between intradiscal saline or methylprednisolone injection at 12-month follow-up [50]. The other small trial ($N=15$) found no differences between intradiscal injections of glycerol and bupivacaine in patients with chronic low back pain in which discography had suggested one symptomatic disc [53].

Adverse effects

In general, few side effects were reported by the studies on epidural and local injection therapy with anaesthetics or steroids. The use of morphine was often associated with side effects such as pruritus, nausea and vomiting. The most common adverse events reported in the prolotherapy trials were temporary increases in back pain and stiffness following injections, reported by nearly all participants at some point in three studies [52, 72, 97].

Radiofrequency denervation

Since Shealy published his first article on radiofrequency denervation of the lumbar zygapophyseal joints in 1975, the technique has been modified and used with varying indications [84].

Effectiveness for acute low back pain

No trials were identified.

Effectiveness for chronic low back pain

Radiofrequency denervation vs sham treatment for chronic facet joint pain The Cochrane review included three trials that showed conflicting evidence on the short-term effect of radiofrequency lesioning on pain and disability [34, 57, 93]. One trial found that radiofrequency denervation statistically significantly reduced pain intensity and improved functioning at 2 month follow-up [93]. Another trial showed greater improvement in Roland–Morris score but not in either Oswestry score or pain score at 4 week follow-up [57]. At 12 weeks, neither functional disability nor pain level showed any treatment effect. The result of the third trial remained unclear since no intention-to-treat analysis was performed [34].

Radiofrequency denervation vs sham treatment for chronic discogenic low back pain One trial did not find any differences between radiofrequency denervation and sham at 8 weeks [2].

Adverse effects

There were no reported adverse effects in most of the trials. Two studies reported some subsiding pain and numbness associated with the procedure [60, 92]. The symptoms were more common and lasted longer in the radiofrequency lesion group. One study reported complaints of subsiding neuritis and slight loss of muscle strength in the hand or arm on the treated side [86]. There were, however, no permanent complications reported.

Surgical interventions for degenerative lumbar spondylosis

The term degenerative lumbar spondylosis is used for degenerative conditions affecting the lumbar spine. These are variously described as lumbar spondylosis or degenerative disc disease; whether or not they are regarded as the effects of ageing, secondary to trauma or ‘wear and tear’, or degenerative disease; and whether they involve the inter-vertebral discs, the vertebrae and/or the associated joints. This includes the associated pathologies or clinical syndromes of instability, spinal stenosis and/or degenerative spondylolisthesis.

Symptoms associated with degenerative lumbar spondylosis are variable in severity and have a relatively low correlation with the severity of radiological changes. Surgical treatment might be either the fusion with the

goal of relieving discogenic and facet pain, and/or decompression of nerve root or the cauda equina compression with the goal of relieving the radiating pain and neurogenic claudication. Generally, fusion is considered if there is severe disc degeneration, misalignment or symptoms and signs of spinal instability.

Effectiveness for acute low back pain

No trials were identified that presented data for acute low back pain separately.

Effectiveness for chronic low back pain

The recently updated Cochrane review included 31 RCTs of all forms of surgical treatment for degenerative lumbar spondylosis [37]. From a surgical perspective, the trials were categorised into three sections: (1) surgical treatment (decompression with or without fusion) for spinal stenosis and/or nerve-root compression; (2) surgical treatment (fusion, intradiscal electrotherapy or disc arthroplasty) for back pain; (3) comparison of different techniques of spinal fusion.

Surgical treatment for spinal stenosis and/or nerve-root compression The effectiveness of surgical decompression for spinal stenosis has been considered in one new trial [1]. In this study, 31 patients were randomised between surgical treatment and conservative therapy. There were no statistically significant differences in the second procedures. At 10 years, five people of the 11 randomised to decompression had no, or minimal, pain compared with the four of 14 who were initially treated conservatively (six were lost to follow-up).

One trial did not find any difference in the clinical outcomes or spondylolisthesis progression between laminectomy and multiple laminotomy for spinal stenosis [74]. This study had several confounding factors. Nine of the 35 patients scheduled for laminotomy actually had a laminectomy for technical reasons and several patients in each group also had an inter-transverse arthrodesis for degenerative spondylolisthesis.

Three trials considered whether some form of posterolateral fusion, with or without instrumentation, was a useful adjunct to decompression alone [9, 40, 45]. Pooling of the three trials ($N=139$) showed no statistically significant difference in the outcomes between decompression plus fusion or decompression alone (random OR 0.44; 95% CI 0.13–1.48), as rated by the surgeon, 18–24 months after the procedure. Lack of power limits definitive conclusions.

The Cochrane review included two trials of surgical treatment for isthmic spondylolisthesis. In one trial patients ($N=111$) treated surgically had less pain and disability than conservative treatment in the form of an

intensive exercise programme, and better self- and observer-rated outcomes at 2 years [66, 67]. There was no significant difference in occupational outcomes. However, no separate data were presented for back pain (one-third) and sciatica (two-third). The other trial compared the results of fusion alone, or fusion plus laminectomy and decompression for isthmic L5/S1 spondylolisthesis [13]. Patients had both back and leg pain, although without serious neurology. The addition of decompression to the arthrodesis did not improve clinical outcomes.

Surgical treatment for back pain The Cochrane review included two trials on the effectiveness of fusion for chronic back pain, compared with conservative treatment [11, 32, 49]. The Swedish trial ($N=294$) compared lumbar fusion with physiotherapy [32]. Patients were recruited who had low back pain for more than 2 years, and no evidence of nerve root compression. All patients had previous physiotherapy without success, and 19% had previous surgery. Patients were randomised to physiotherapy ($N=72$) and one of three different fusion techniques ($N=222$). Surgery resulted in statistically significantly greater effects on pain, disability, overall improvement and return to work. There were no significant differences in any of these outcomes between the three surgical groups. A limitation of this study was the control group that received usual conservative treatment that had already failed.

The Norwegian trial compared posterolateral fusion with transpedicular screws and post-operative physiotherapy vs a modern 'rehabilitation' type of programme, consisting of an educational intervention and a 3-week course of intensive exercise sessions, based on cognitive-behavioural principles [11]. Sixty-four patients with low back pain, lasting longer than 1 year plus disc degeneration at L4/5 and/or L5/S1 [11], and a further 60 patients with chronic low back pain more than 1 year after previous discectomy [49] were randomised and reported on separately. There were no significant differences in any of the main outcomes of independent observer rating, patient rating, pain, disability or return to work at 1 year follow-up.

The European guidelines included a third trial [26]. This UK trial ($N=349$) found no statistically or clinically significant differences in pain, disability and quality of life between spinal fusion and an intensive 15-day programme of exercise therapy, spine stabilisation exercises and education using cognitive-behavioural principles at the two-year follow-up.

The Cochrane review also identified three small RCTs of intradiscal electrotherapy (IDET) for degenerative lumbar spondylosis. Two trials reported poor outcomes. One trial reported success in only one patient in the IDET group ($N=13$) and two in the placebo group ($N=15$) at 8 weeks follow-up [2]. The other

trial ($N=57$) reported that no patient in either arm met the pre-defined criteria for a clinically significant improvement or a successful outcome [31]. However, the third trial ($N=64$) reported a significantly greater improvement in pain and disability with IDET [73].

The Cochrane review did not identify any published RCTs on artificial discs.

A comparison of different techniques of spinal fusion The Cochrane review included 14 trials on instrumentation in fusion. Studies were heterogeneous in terms of study populations and techniques of instrumentation. Studies also varied in the outcome measures used, with the most common being the technical surgical outcomes—fusion rates, progression of spondylolisthesis and re-operation rates.

Eight trials directly addressed the question of whether instrumentation improves the outcome of posterolateral fusion, with an average 95% of patient follow-up at 16 months to 4.5 years [9, 28, 29, 32, 65–67, 88, 99]. The pooled effect of eight trials ($N=638$) showed that instrumentation improves the fusion rate (random OR 0.43; 95% CI 0.21–0.91), but instrumentation does not produce statistically or clinically significant improvement in the clinical outcomes (random OR 0.64; 95% CI 0.35–1.17).

Four trials compared various combinations of anterior, posterior or combined fusion [17, 51, 80, 81]. One trial found no difference in the clinical outcomes between anterior lumbar interbody fusion (ALIF) plus pedicle screws plus instrumented posterolateral fusion (360°) vs ALIF plus pedicle screws without graft (270°) [81]. Another trial found no difference in the outcomes with the addition of a posterior lumbar interbody fusion in degenerative spondylolisthesis (Grade I/II) to a posterolateral instrumented fusion for patients over 60 years of age, but significantly longer surgery time, higher blood loss and complication rate in this group [51]. The third trial found that circumferential fusion using ALIF carbon fibre cages produced a higher fusion rate (90 vs 80%) and lower re-operation rate (7 vs 22%) than posterolateral fusion with Cotrel–Dubouset instrumentation [17]. The last trial found a greater fusion rate using a cylindrical threaded titanium cage inserted anteriorly compared with the trial using a femoral ring allograft, but there were no differences on disability and neurologic outcome. These conflicting results do not permit any conclusions about the relative effectiveness of anterior, posterior or circumferential fusion.

The Cochrane review also identified four trials that assessed whether electrical stimulation could enhance the fusion. Three trials in non-instrumented fusion showed a significant effect on the fusion rate (random OR 0.38; 95% CI 0.22–0.64). Two out of three trials in instrumented fusion showed positive results though the

third trial had negative results (random OR 0.59; 95% CI 0.15–2.30). Three studies did not find a difference in the clinical outcomes [39, 47, 68]. Interpretation of these results is hampered by the heterogeneity in the fusion technique.

Surgery and other invasive treatments for disc prolapse

The primary rationale of any form of surgery for disc prolapse is to relieve the nerve-root irritation or compression due to herniated disc material. Open discectomy, performed with (micro-), or without use of an operating microscope, is the most common procedure, but there are some other less-invasive surgical techniques. Chemonucleolysis (dissolution of the nucleus by enzyme injection) using chymopapain was at one stage advocated for contained lumbar disc prolapse, i.e. without fragment sequestration into the spinal canal.

Effectiveness for acute and chronic sciatica

The Cochrane review did not clearly distinguish between acute and chronic sciatica, because it was not possible to analyse the patients according to the duration of their symptoms.

Chemonucleolysis vs placebo The Cochrane review included five trials that compared chemonucleolysis using chymopapain vs placebo, for patients with positive myelogram for disc herniation and failed conservative treatment [21, 27, 30, 46, 82]. The results showed that chymopapain was more effective than placebo rated by patients (OR 0.24; 95% CI 0.12–0.49) and observers (OR 0.40; 95% CI 0.21–0.75). Fewer patients after chymopapain injection proceeded to open discectomy (OR 0.41; 95% CI 0.25–0.68).

Chemonucleolysis vs other interventions The Cochrane review included five trials that compared chemonucleolysis using chymopapain vs surgical discectomy [19, 24, 56, 69, 91]. The results showed consistently poorer results with chemonucleolysis, but this was not statistically significant. About 30% of patients with chemonucleolysis had further disc surgery within 2 years, and meta-analysis showed that a second procedure was much more likely after chemonucleolysis (OR 0.07; 95% CI 0.02–0.18).

No statistically significant differences were demonstrated between low-dose and standard-dose chymopapain [4], between chymopapain and collagenase [43] or between chymopapain and steroid injections [5, 6]. It should be noted that although one trial suggested that collagenase was more effective than placebo, that was a small study and there was a 40% code break by 8 weeks [10].

Surgical discectomy vs conservative treatment There was only one trial that compared the surgical treatment of lumbar disc prolapse with conservative treatment [96]. The trial was not blinded and there was considerable crossover. Both the patient- and observer-ratings showed that discectomy was significantly better than 'conservative therapy' at 1 year, but there were no significant differences in the outcomes at 4 and 10 years.

Microdiscectomy vs standard discectomy Three trials, with data from 219 patients, compared microdiscectomy with standard discectomy [44, 55, 89]. Use of the microscope lengthened the operative procedure, but did not appear to make any significant difference due to peri-operative bleeding or other complications, length of in-patient stay or the formation of the scar tissue. There were no differences in the clinical outcomes and duration of sick leave.

Automated percutaneous discectomy vs other procedures Two trials compared the automated percutaneous discectomy with microdiscectomy. These trials were not directly comparable, as one used a modified forceps and an automated cutter with suction [64] and the other used an automated suction nucleotome alone [16]. One trial ($N=40$) showed that the clinical outcomes were comparable to microdiscectomy, but considered that only 10–15% of the patients needing surgical treatment might be suitable for automated percutaneous discectomy [64]. The other trial ($N=71$) reported only 29% satisfactory results for automated percutaneous discectomy compared with 80% for microdiscectomy [16]. One other trial ($N=141$) found automated percutaneous discectomy to be inferior to chemonucleolysis on patient rating of improvement and second procedures after 6 months [75].

Discussion

The evidence on the effectiveness of the injection therapy showed that there is insufficient evidence on the effectiveness of injection therapy. Facet joint, epidural and trigger point injections have not clearly been shown to be effective, nor is there strong evidence that these injections are ineffective. Because of the lack of statistically significant results as well as the lack of well-designed trials, a solid foundation for the effectiveness of injection therapy is lacking.

There is conflicting evidence for the effectiveness of radiofrequency denervation for lumbar facet joint pain. There is limited evidence suggesting that intradiscal radiofrequency denervation may not be effective in relieving the discogenic low back pain. Further, high-quality RCTs are needed, with larger patient samples and data on long-term effects, for which the current evidence is inconclusive.

Surgical discectomy provides effective clinical relief for carefully selected patients with sciatica due to lumbar disc prolapses that fail to resolve with conservative management. There is no evidence supporting the choice of micro- or standard discectomy based on more favourable clinical outcomes. Strong evidence exists that although better than placebo, the overall results of chemonucleolysis are poorer than those of primary discectomy.

There is insufficient evidence on the effectiveness of surgery for degenerative lumbar spondylosis on clinical outcomes to draw any firm conclusions. Three trials comparing fusion surgery with conservative treatment for chronic low back pain showed conflicting findings [11, 26, 32, 49]. The trials all used physiotherapy as a control, but in the Swedish Lumbar Spine Study, the patients were treated with different kinds of physical therapy that were similar to the treatment, the patients already received, without any success and before a decision on the operative treatment was made [32]. The conservative treatment arm may thus have been close to the natural history of the disease. This may explain why the Swedish trial found a difference in the effect in favour of surgery. The other two trials that found no or only small differences between surgery and conservative treatment used an active rehabilitation programme with the current standards of care as a control intervention. These studies reported 1–2 year follow-up results. Longer follow-up is needed to give insight into the long-term effectiveness. As there are only three trials with conflicting results on the effectiveness, there is clearly a need for further randomised studies.

For this overview on effectiveness of surgery and other invasive procedures for low back pain, evidence was used from the latest issue of the Cochrane Library, issue 2, 2005. Only one of the relevant Cochrane reviews had been updated: surgery for degenerative lumbar spondylosis [37]. The other Cochrane reviews had search dates ranging from 1996 to January 2004. Consequently, these reviews did not include the most recent trials. The mission of the Cochrane Collaboration is to provide up-to-date information on the effectiveness of medical interventions for decision makers at all levels. The Cochrane Back Review Group aims to regularly update the reviews. The Cochrane Library is the single most authoritative source of this kind of information. Thus, it is worrisome that some of the Cochrane reviews may be out-of-date and lack relevant scientific evidence. To provide an up-to-date summary of the evidence, the recently updated evidence summary of the COST B13 European Guidelines for the Management of Acute and Chronic Low Back Pain was used for identification of additional trials that were not included in the Cochrane reviews.

Implications for further research

There is a dire need for updating the Cochrane reviews on invasive treatments for low back pain. High-quality surgical trials are still needed to provide further evidence on the clinical efficacy and cost-effectiveness of surgical decompression and/or fusion for specific syndromes associated with degenerative lumbar spondylosis. These trials should preferably compare surgical treatments with natural history, placebo or conservative treatment.

Future trials should also conduct an economic evaluation alongside, because there are major gaps in our knowledge of the costs and cost-effectiveness of all forms of surgical treatment for lumbar degenerative spondylosis and disc prolapse. Due to limited health care budgets, economic evaluations are becoming increasingly important. In economic evaluations both costs and effects of the intervention and relevant alternatives are taken into account. Not only patients, health-care providers and insurance companies may benefit from economic evaluations. Especially, policy-makers can use economic evaluations in the decision-making process.

Economic evaluations answer the question if an intervention is worth doing compared with other interventions. They do not necessarily answer the question what the cheapest intervention is. If an intervention is more effective than another intervention but associated with higher costs, the intervention may still be used by health-care providers and patients and may still be reimbursed by insurers. This seems especially relevant to surgical interventions, because they are usually associated with higher costs compared with conservative treatments.

Implications for clinical practice

Facet joint, epidural, trigger point and sclerosant injections have not clearly been shown to be effective and can consequently not be recommended.

Surgical discectomy may be considered for selected patients with sciatica due to lumbar disc prolapses that fail to resolve with conservative management.

The three trials show conflicting results on the effectiveness of surgery for chronic low back pain: one trial is effective when compared to ordinary physiotherapy and two trials are not superior to the intensive conservative treatment. Thus, a combination of cognitive intervention and exercises is recommended, when available.

Fusion surgery for chronic low back pain may be considered only in carefully selected patients with severe pain after the active rehabilitation programmes during the two-year time have failed. Cognitive intervention

combined with exercises is recommended when available. Demanding surgical techniques are not better than the traditional posterolateral fusion without internal fixation.

There is no scientific evidence on the effectiveness of spinal stenosis surgery. In the case of severe spinal

stenosis with progressive neurologic deficits and severe neurogenic claudication, clinical experience clearly indicates surgery.

There are still only preliminary results available on disc replacement and artificial discs, preventing any conclusions.

References

- Amundsen T, Weber H, Nordal HJ, Magnaes B, Abdelnoor M, Lilleas F (2000) Lumbar spinal stenosis: conservative or surgical management? A prospective 10-year study. *Spine* 25:1424–1435
- Barendse GAM, van den Berg SGM, Kessels AHF, Weber WEJ, van Kleef M (2001) Randomized controlled trial of percutaneous intradiscal radiofrequency thermocoagulation for chronic discogenic back pain: lack of effect from a 90-second 70 C lesion. *Spine* 26:287–292
- Béliveau P (1971) A comparison between epidural anaesthesia with and without corticosteroid in the treatment of sciatica. *Rheumatol Phys Med* 11:40–43
- Benoist M, Bonneville JF, Lassale B, Runge M, Gillard C, Vazquez Suarez J, Deburge A (1993) A randomized, double-blind study to compare low-dose with standard-dose chymopapain in the treatment of herniated lumbar intervertebral discs. *Spine* 18:28–34
- Bontoux D, Alcalay M, Debiais F, Garrouste O, Ingrand P, Azais I, Roualdes G (1990) Treatment of lumbar disk hernia by intra-disk injection of chymopapain or triamcinolone hexacetonide. Comparative study of 80 cases [Traitement des hernies discales lombaires par injection intradiscale de chymopapaine ou d'hexacetonide de triamcinolone. Etude comparee de 80 cas]. *Rev Rhum Mal Osteoartic* 57:327–331
- Bourgeois P, Benoist M, Palazzo E, Belmatoug N, Folinais D, Frot B, Busson G, Lassale P, Montagner C, Binoche T (1988) Multicenter randomized double-blind study of triamcinolone hexacetonide versus chymopapain in the treatment of disk lumbosciatica. Initial results at 6 months [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]. *Rev Rhum Mal Osteoartic* 55:767–769
- Bouter LM, Pennick V, Bombardier C, Editorial Board of the Back Review Group (2003) *Cochrane Back Review Group*. *Spine* 28:1215–1218
- Breivik H, Hesla PE, Molnar I, Lind B (1976) Treatment of chronic low back pain and sciatica: comparison of caudal epidural injections of bupivacaine and methylprednisolone with bupivacaine followed by saline. *Adv Pain Res Ther* 1:927–932
- Bridwell KH, Sedgewick TA, O'Brien MF, Lenke LG, Baldus C (1993) The role of fusion and instrumentation in the treatment of degenerative spondylolisthesis with spinal stenosis. *J Spinal Disord* 6:461–472
- Bromley JW, Varma AO, Santoro AJ, Cohen P, Jacobs R, Berger L (1984) Double-blind evaluation of collagenase injections for herniated lumbar discs. *Spine* 9:486–488
- Brox JI, Sorensen R, Friis A, Nygaard O, Indahl A, Keller A, Ingebrigtsen T, Eriksen HR, Holm I, Koller AK, Riise R, Reikerus O (2003) Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. *Spine* 28:1913–1921
- Bush K, Hillier S (1991) A controlled study of caudal epidural injections of triamcinolone plus procaine for the management of intractable sciatica. *Spine* 15:572–575
- Carragee EJ (1997) Single-level posterolateral arthrodesis, with or without posterior decompression, for the treatment of isthmic spondylolisthesis in adults. A prospective, randomised study. *J Bone Joint Surg* 79A:1175–1180
- Carette S, Marcoux S, Truchon R, Grondin C, Gagnon J, Allard Y, Lattulippe M (1991) A controlled trial of corticosteroid injections into facet joints for chronic low back pain. *New Engl J Med* 325:1002–1007
- Carette S, Leclaire R, Marcoux S (1997) Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *New Engl J Med* 336:1634–1640
- Chatterjee S, Foy PM, Findlay GF (1995) Report of a controlled clinical trial comparing automated percutaneous lumbar discectomy and microdiscectomy in the treatment of contained lumbar disc herniation. *Spine* 20:734–738
- Christensen FB, Hansen ES, Eiskjaer SP, Hoy K, Helmig P, Neumann P, Niedermann B, Bunger CE (2002) Circumferential lumbar spinal fusion with ALIF Brantigan cage versus posterolateral fusion with titanium CD-Horizon: a prospective, randomized, clinical study of 146 patients. *Spine* 27:2674–2683
- Collée G, Dijkmans BAC, Vandendroucke JP, Cats A (1991) Iliac crest pain syndrome in low back pain. A double blind, randomized study of local injection therapy. *J Rheumatol* 18:1060–1063
- Crawshaw C, Frazer AM, Merriam WF, Mulholland RC, Webb JK (1984) A comparison of surgery and chemonucleolysis in the treatment of sciatica. A prospective randomized trial. *Spine* 9:195–198
- Cuckler JM, Bernini PA, Wiesel SW, Booth RE, Rothman RH, Pickens GT (1985) The use of epidural steroids in the treatment of lumbar radicular pain. *J Bone Joint Surg* 67A:63–66
- Dabezies EJ, Langford K, Morris J, Shields CB, Wilkinson HA (1988) 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* 13:561–565
- Dallas TL, Lin RL, Wu WH, Wolske P (1987) Epidural morphine and methylprednisolone for low-back pain. *Anesthesiology* 67:408–411
- Dechow E, Davies RK, Carr AJ, Thompson PW (1999) A randomized, double-blind, placebo-controlled trial of sclerosing injections in patients with chronic low back pain. *Rheumatology (Oxford)* 38:1255–1259

24. Ejeskar A, Nachemson A, Herberts P, Lysell E, Andersson G, Irstam L, Peterson LE (1983) Surgery versus chemonucleolysis for herniated lumbar discs. A prospective study with random assignment. *Clin Orthop* 174:236–242
25. Fairbank J (1999) Spine update: randomized controlled trials in the surgical management of spinal problems. *Spine* 24:25–56
26. Fairbank JC, Frost H, Wilson-MacDonald J, Yu LM, Barker K, Collins R (2005) Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. *BMJ* 330:1233
27. Feldman J, Menkes CJ, Pallardy G, Chevrot A, Horreard P, Zenny JC, Godefroy D, Amor B (1986) Double-blind study of the treatment of disc lumbosciatica by chemonucleolysis [Etude en double-aveugle du traitement de la lumbosciatique discale par chimionucleolyse]. *Rev Rhum Mal Osteoartic* 53:147–152
28. Fischgrund JS, Mackay M, Herkowitz HN, Brower R, Montgomery DM, Kurz LT (1997) Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective, randomized study comparing decompressive laminectomy and arthrodesis with and without spinal instrumentation. *Spine* 22:2807–2812
29. France JC, Yaszemski MJ, Lauerman WC, Cain JE, Glover JM, Lawson KJ, Coe JD, Topper SM (1999) A randomized prospective study of posterolateral lumbar fusion: outcomes with and without pedicle screw instrumentation. *Spine* 24:553–560
30. Fraser RD (1982) Chymopapain for the treatment of intervertebral disc herniation. A preliminary report of a double-blind study. *Spine* 7:608–612
31. Freeman BJC, Fraser RD, Cain CMJ, Hall DJ (2003) A randomised double-blind controlled efficacy study: intradiscal electrothermal therapy (IDET) versus placebo. *J Bone Joint Surg* 85B(Suppl III):280
32. Fritzell P, Hagg O, Wessberg P, Nordwall A (2001) Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. *Spine* 26:2521–2532
33. Frost FA, Jessen B, Siggaard-Andersen J (1980) A control, double-blind comparison of mepivacaine injection versus saline injection for myofascial pain. *Lancet* 1(8167):499–500
34. Gallagher J, Petriccione di Vadi PL, Wedley JR (1994) Radiofrequency facet joint denervation in the treatment of low back pain: a prospective controlled double-blind study to assess its efficacy. *Pain Clin* 7:193–198
35. Garvey TA, Marks MR, Wiesel SW (1989) A prospective, randomized, double-blind evaluation of trigger-point injection therapy for low-back pain. *Spine* 14:962–964
36. Gibson JN, Grant IC, Waddell G (2000) Surgery for lumbar disc prolapse. *Cochrane Database Syst Rev*, Issue 3
37. Gibson JNA, Waddell G (2005) Surgery for degenerative lumbar spondylosis. *Cochrane Database Syst Rev*, Issue 2
38. Glynn Ch, Dawson D, Sanders R (1988) A double-blind comparison between epidural morphine and epidural clonidine in patients with chronic non-cancer pain. *Pain* 34:123–128
39. Goodwin CB, Brighton CT, Guyer RD, Johnson JR, Light KI, Yuan HA (1999) A double-blind study of capacitively coupled electrical stimulation as an adjunct to lumbar spinal fusions. *Spine* 24:1349–1357
40. Grob D, Humke T, Dvorak J (1995) Degenerative lumbar spinal stenosis. Decompression with and without arthrodesis. *J Bone Joint Surg* 77A:1036–1041
41. Hameroff SR, Crago BR, Blitt CD, Womble J, Kanel J (1981) Comparison of bupivacaine, etidocaine, and saline for trigger-point therapy. *Anaesth Analg* 60:752–755
42. Heavner JE, Racz GB, Raj P (1999) Percutaneous epidural neuroplasty: prospective evaluation of 0.9% NaCl versus 10% NaCl with or without hyaluronidase. *Reg Anesth Pain Med* 24:202–207
43. Hedtmann A, Fett H, Steffen R, Kramer J (1992) Chemonucleolysis using chymopapain and collagenase. 3-Year results of a prospective randomized study [Chemonukleolyse mit Chymopapain und Kollagenase. 3-Jahres-Ergebnisse einer prospektiv-randomisierten Studie]. *Z Orthop Ihre Grenzgeb* 130:36–44
44. Henrikson L, Schmidt V, Eskesen V, Jantzen E (1996) A controlled study of microsurgical versus standard lumbar discectomy. *Br J Neurosurg* 10:289–293
45. Herkowitz HN, Kurz LT (1991) Degenerative lumbar spondylolisthesis with spinal stenosis. A prospective study comparing decompression with decompression and intertransverse process arthrodesis. *J Bone Joint Surg Am* 73A:802–808
46. Javid MJ, Nordby EJ, Ford LT, Hejna WJ, Whisler WW, Burton C (1983) Safety and efficacy of chymopapain (chymodiactin) in herniated nucleus pulposus with sciatica. *JAMA* 249:2489–2494
47. Jenis LG, An HS, Stein R, Young B (2000) Prospective comparison of the effect of direct current electrical stimulation and pulsed electromagnetic fields on instrumented posterolateral lumbar arthrodesis. *J Spinal Disord* 13:290–296
48. Karppinen J, Malmivaara A, Kurunlahti M, Kyllonen E, Pienimäki T, Nieminen P, Ohinmaa A, Tervonen O, Vanharanta H (2001) Periradicular infiltration for sciatica: a randomized controlled trial. *Spine* 26:1059–1067
49. Keller A, Brox JI, Gunderson R, Holm I, Friis A, Reikeras O (2004) Trunk muscle strength, cross-sectional area and density in patients with chronic low back pain randomized to lumbar fusion or cognitive intervention and exercises. *Spine* 29:3–8
50. Khot A, Bowditch M, Powell J, Sharp D (2004) The use of intradiscal steroid therapy for lumbar spinal discogenic pain: a randomized controlled trial. *Spine* 29:833–836
51. Kitchel SH, Matteri RE (2002) Prospective randomized evaluation of PLIF in degenerative spondylolisthesis patients over 60 years old. *Curr Concepts Rev*
52. Klein RG, Eek BC, DeLong WB, Mooney V (1993) A randomized double-blind trial of dextrose-glycerin-phenol injections for chronic, low back pain. *J Spinal Disord* 6:23–33
53. Kotilainen E, Muittari P, Kirvelä O (1997) Intradiscal glycerol or bupivacaine in the treatment of low back pain. *Acta Neurochir (Wien)* 139:541–545
54. Kraemer J, Ludwig J, Bickert U, Owczarek V, Traupe M (1997) Lumbar epidural perineural injection: a new technique. *Eur Spine J* 6:357–361
55. Lagarrigue J, Chaynes P (1994) Comparative study of disk surgery with or without microscopy. A prospective study of 80 cases [Etude comparative de la chirurgie discale avec et sans microscope]. *Neurochirurgie* 40:116–120
56. Lavignolle B, Vital JM, Baulny D, Grenier F, Castagnera L (1987) Comparative study of surgery and chemonucleolysis in the treatment of sciatica caused by a herniated disk [Etudes comparees de la chirurgie et de la chimionucleolyse dans le traitement de la sciatique par hernie discale]. *Acta Orthop Belg* 53:244–249

57. Leclaire R, Fortin L, Lambert R (2001) Radiofrequency facet joint denervation in the treatment of low back pain: a placebo-controlled clinical trial to assess efficacy. *Spine* 26:1411–1416
58. Lilius G, Lassonen AM, Myllynen P, Harilainen A, Salo L (1989) The lumbar facet joint syndrome—significance of inappropriate signs. A randomized, placebo controlled trial. *French J Orthop Surg* 3:479–486
59. Lilius G, Harilainen A, Laasonen EM, Myllynen P (1990) Chronic unilateral low back pain. Predictors of outcome of facet joint injections. *Spine* 15:780–782
60. Lord SM, Barnsley L, Wallis BJ (1996) Percutaneous radio-frequency neurotomy for chronic cervical zygapophyseal joint pain. *N Engl J Med* 335:1721–1726
61. Lutze M, Stendel R, Vesper J, Brock M (1997) Periradicular therapy in lumbar radicular syndromes: methodology and results. *Acta Neurochir (Wien)* 139:719–724
62. Marks RC, Houston T, Thulbourne T (1992) Facet joint injection and facet nerve block: a randomised comparison in 86 patients with chronic low back pain. *Pain* 49:325–328
63. Mathews JA, Mills SB, Jenkins VM, Grimes SM, Morkel MJ, Mathews W, Scott CM, Sittampalam Y (1987) Back pain and sciatica: controlled trials of manipulation, traction, sclerosant and epidural injections. *Br J Rheum* 26:416–423
64. Mayer HM, Brock M (1993) Percutaneous endoscopic discectomy: surgical technique and preliminary results compared to microsurgical discectomy. *J Neurosurg* 78:216–225
65. McGuire RA, Amundson GM (1993) The use of primary internal fixation in spondylolisthesis. *Spine* 18:1662–1672
66. Moller H, Hedlund R (2000) Surgery versus conservative management in adult isthmic spondylolisthesis—a prospective randomized study: part 1. *Spine* 25:1711–1715
67. Moller H, Hedlund R (2000) Instrumented and noninstrumented posterolateral fusion in adult spondylolisthesis—a prospective randomized study: part 2. *Spine* 25:1716–1721
68. Mooney V (1990) A randomized double-blind prospective study of the efficacy of pulsed electromagnetic fields for interbody lumbar fusions. *Spine* 15:708–712
69. Muralikuttan KP, Hamilton A, Kernohan WG, Mollan RA, Adair IV (1992) A prospective randomized trial of chemonucleolysis and conventional disc surgery in single level lumbar disc herniation. *Spine* 17:381–387
70. Nelemans PJ, de Bie RA, de Vet HC, Sturmans F (2000) Injection therapy for subacute and chronic benign low back pain. *Cochrane Database Syst Rev*, Issue 2
71. Niemisto L, Kalso E, Malmivaara A, Seitsalo S, Hurri H (2003) Radiofrequency denervation for neck and back pain: a systematic review within the framework of the Cochrane collaboration back review group. *Spine* 28:1877–1888
72. Ongley MJ, Klein RG, Dorman TA, Eek BC, Hubert LJ (1987) A new approach to the treatment of chronic low back pain. *Lancet* 2(8551):143–146
73. Pauza KJ, Howell S, Dreyfuss P, Pelozo JH, Dawson K, Bogduk N (2004) A randomized, placebo-controlled trial of intradiscal electrothermal therapy for the treatment of discogenic low back pain. *Spine J* 4:27–35
74. Postacchini F, Cinotti G, Perugia D, Gumina S (1993) The surgical treatment of central lumbar stenosis. *J Bone Joint Surg* 75B:386–392
75. Revel M, Payan C, Vallee C, Laredo JD, Lassale B, Roux C (1993) Automated percutaneous lumbar discectomy versus chemonucleolysis in the treatment of sciatica. A randomized multicenter trial. *Spine* 18:1–7
76. Riew KD, Yin Y, Gilula L, Bridwell KH, Lenke LG, Laurusen C, Goette K (2000) The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double-blind study. *J Bone Joint Surg* 82A:1589–1593
77. Rocco AG, Frank E, Kaul AF, Lipson SJ, Gallo JP (1989) Epidural steroids, epidural morphine and epidural steroids combined with morphine in the treatment of post-laminectomy syndrome. *Pain* 36:297–303
78. Rogers P, Nash T, Schiller D, Norman J (1992) Epidural steroids for sciatica. *Pain Clin* 5:67–72
79. Samwel H, Slappendel R, Crul BJ (2000) Psychological predictors of the effectiveness of radiofrequency lesioning of the cervical spinal dorsal ganglion (RF-DRG). *Eur J Pain* 4:149–155
80. Sasso RC, Kitchel SH, Dawson EG (2004) A prospective, randomized controlled clinical trial of anterior lumbar interbody fusion using a titanium cylindrical threaded fusion device. *Spine* 29:113–122
81. Schofferman J, Slosar P, Reynolds J, Goldthwaite N, Koestler M (2001) A prospective randomized comparison of 270° fusions to 360° fusions (circumferential fusions). *Spine* 26:E207–E212
82. Schwetschenau R, Ramirez A, Johnston J, Barnes E, Wiggs C, Martins AN (1976) Double-blind evaluation of intradiscal chymopapain for herniated lumbar discs. Early results. *J Neurosurg* 45:622–627
83. Serrao JM, Marks RL, Morley SJ, Goodchild CS (1992) Intrathecal midazolam for the treatment of chronic mechanical low back pain: a controlled comparison with epidural steroid in a pilot study. *Pain* 48:5–12
84. Shealy CN (1975) Percutaneous radiofrequency denervation of spinal facets. Treatment for chronic back pain and sciatica. *J Neurosurg* 43:448–451
85. Simmons JW, McMillin JN, Emery SF, Kimmich SJ (1992) Intradiscal steroids: a prospective double-blind clinical trial. *Spine* 17:172–175
86. Slappendel R, Crul BJ, Braak GJ (1997) The efficacy of radiofrequency lesioning of the cervical spinal dorsal root ganglion in a double blinded randomized study: no difference between 40 degrees C and 67 degrees C treatments. *Pain* 73:159–163
87. Sonne M, Christensen K, Hansen SE, Jensen EM (1985) Injection of steroids and local anaesthetics as therapy for low-back pain. *Scand J Rheum* 14:343–345
88. Thomsen K, Christensen FB, Eiskjaer SP, Hansen ES, Fruensgaard S, Bunger CE (1997) The effect of pedicle screw instrumentation on functional outcome and fusion rates in posterolateral lumbar spinal fusion. A prospective randomized clinical study. *Spine* 22:2813–2822
89. Tullberg T, Isacson J, Weidenhielm L (1993) Does microscopic removal of lumbar disc herniation lead to better results than the standard procedure? Results of a one-year randomized study. *Spine* 18:24–27
90. Vad VB, Bhat AL, Lutz GE, Cammisa F (2002) Transforaminal epidural steroid injections in lumbosacral radiculopathy: a prospective randomized study. *Spine* 27:11–16
91. Van Alphen HA, Braakman R, Bezemer PD, Broere G, Berfelo MW (1989) Chemonucleolysis versus discectomy: a randomized multicenter trial. *J Neurosurg* 70:869–875

-
92. Van Kleef M, Liem L, Lousberg R (1996) Radiofrequency lesion adjacent to the dorsal root ganglion for cervicobrachial pain: a prospective double blind randomized study. *Neurosurgery* 38:1127–1131
93. Van Kleef M, Barendse GA, Kessels A (1999) Randomized trial of radiofrequency lumbar facet denervation for chronic low back pain. *Spine* 24:1937–1942
94. Wallis BJ, Lord SM, Bogduk N (1997) Resolution of psychological distress of whiplash patients following treatment by radiofrequency neurotomy: a randomised, double-blind, placebo-controlled trial. *Pain* 73:15–22
95. Weber H (1978) Lumbar disc herniation. A prospective study of prognostic factors including a controlled trial (see also pp89–120). *J Oslo City Hosp* 28:33–64
96. Weber H (1983) Lumbar disc herniation. A controlled, prospective study with ten years of observation. *Spine* 8:131–140
97. Yelland MJ, Glasziou PP, Bogduk N, Schluter PJ, McKernon M (2004) Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. *Spine* 29:9–16
98. Yelland MJ, Del Mar C, Pirozzo S, Schoene ML (2004) Prolotherapy injections for chronic low back pain: a systematic review. *Spine* 29:2126–2133
99. Zdeblick TA (1993) A prospective, randomized study of lumbar fusion. Preliminary results. *Spine* 18:983–991