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Effectiveness of Spinal Fusion *Versus* Structured Rehabilitation in Chronic Low Back Pain Patients With and Without Isthmic Spondylolisthesis

A Systematic Review

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Study Design. Systematic review.

Objective. To determine if the presence of isthmic spondylolisthesis modifies the effect of treatment (fusion *vs.* multidimensional supervised rehabilitation) in patients with chronic low back pain (CLBP).

Summary of Background Data. Results of spinal surgery for CLBP are variable. It is unclear whether patients with CLBP and isthmic spondylolisthesis have more success with surgery *versus* a multidimensional supervised rehabilitation program when compared with those with CLBP but without spondylolisthesis.

Methods. A systematic search was conducted in MEDLINE and the Cochrane Collaboration Library for articles published through January 2011. Randomized controlled trials (RCTs) were included that compared spine fusion *versus* multidimensional supervised rehabilitation in patients with and without isthmic spondylolisthesis. Standardized mean differences (SMDs) and risk differences were calculated for common outcomes, and then compared to determine potential heterogeneity of treatment effect. The final strength of the body of literature was expressed as "high," "moderate," or "low" confidence that the evidence reflects the true effect.

Results. No studies were found that directly compared the two subgroups. Three RCTs compared fusion with supervised nonoperative care in patients with CLBP without isthmic spondylolisthesis; one RCT evaluated these treatments in patients with isthmic spondylolisthesis. There were study differences in patient characteristics, type of fusion, the nature of the rehabilitation, outcomes assessed, and length of follow-up. The SMDs for pain in favor of fusion were modest at 2 years for those without isthmic spondylolisthesis, but large in favor of fusion for those with isthmic spondylolisthesis compared with rehabilitation. Similarly, the SMDs for function in patients without isthmic spondylolisthesis compared with rehabilitation was small at 2 years, but appreciably higher in favor of fusion in patients with isthmic spondylolisthesis.

Conclusion. The overall strength of evidence evaluating whether the presence of isthmic spondylolisthesis modifies the effect of fusion compared with rehabilitation patients with CLBP is "low." Fusion should be considered for patients with low back pain and isthmic spondylolisthesis who have failed nonoperative treatment.

Clinical Recommendations. We recommend considering fusion for patients with isthmic spondylolisthesis and lower back pain who have failed nonoperative treatment. Recommendation: Weak.

Key words: fusion, heterogeneity of treatment effect, isthmic spondylolisthesis, low back pain, rehabilitation. **Spine 2011; 36:S110–S119**

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Despite years of treatment and debate, the answer as to what is the best treatment for patients with chronic low back pain (CLBP) remains unsettled. Various forms of nonsurgical interventions such as physiotherapy, exercise, and team rehabilitation have been studied but the results appear inconsistent and there remains no strong consensus as to when to use which treatment.[1–4] Similarly, the efficacy of surgical fusions for CLBP remains controversial. Many practitioners refer to studies that patient outcomes, even after well-done posterolateral fusions (PLFs), can be disappointing, with a significant number of individuals continuing to report pain and disability despite high rates of radiographic fusion.[5–11] As rates of fusion have increased substantially over the past two decades,[12] many continue to

suggest that there has not necessarily been an associated improvement in clinical indications or outcomes.

One potential reason for the lack of encouraging results of spinal surgery for CLBP may be in part a result of failing to classify this condition as heterogeneous.[13–15] Results from randomized controlled trials (RCTs) represent average effects (population means), and, while estimates of the average treatment effect are useful, some individuals will respond more positively (efficacy) or more negatively (safety) than the reported average. Such variation in results is termed heterogeneity of treatment effects (HTE).[16] When the same treatment results in different outcomes in different patients, HTE is present. One way to identify HTE is to analyze the effect of treatment in subgroups of patients with certain baseline characteristics.

One subgroup of patients with CLBP that may respond differently to lumbar fusion is the group with isthmic spondylolisthesis. A few studies suggest that fusion outcomes in this group may be better than outcomes achieved in patients with low back pain (LBP) without isthmic spondylolisthesis.[17,18] To date, however, there have been no direct comparisons between the two as to whether surgery is more successful in one subgroup as opposed to the other, or whether either condition necessarily responds better to an operative intervention *versus* a supervised rehabilitation program. Therefore, we set out to review the literature regarding the surgical and nonsurgical treatment of patients with CLBP with and without isthmic spondylolisthesis. Our question was whether the presence of isthmic spondylolisthesis modifies the effect of treatment (fusion *vs.* supervised rehabilitation) in patients with CLBP.

MATERIALS AND METHODS

Electronic Literature Search

A systematic search was conducted in MEDLINE and the Cochrane Collaboration Library for literature published through January 2011. We limited our results to humans and to articles published in the English language. Reference lists of included articles were also systematically checked. To evaluate whether the effects of treatment in LBP patients were modified by the presence of isthmic spondylolisthesis, we first sought RCTs evaluating surgical fusion *versus* supervised rehabilitation for patients with CLBP that contained subpopulations of patients with and without isthmic spondylolisthesis. Having found none, we then searched the literature for RCTs that compared spine fusion *versus* supervised rehabilitation among those within a specific subgroup of patients with CLBP patients (*i.e.*, among those with isthmic spondylolisthesis only) to compare with other RCTs that were conducted among patients in the other subgroup (*i.e.*, among those without isthmic spondylolisthesis). We excluded studies comparing surgery other than fusion to supervised rehabilitation, surgery *versus* surgery; case series (a series of patients all receiving the same treatment) were also excluded. In addition, articles were excluded if they had either (*a*) significant dropout of eligible participants; (*b*) excluded eligible patients for criteria other than standard acceptable entrance characteristics; or (*c*) failed to describe a supervised nonoperative program. Articles were excluded if they were pediatric studies (<18 years of age), or if they included patients with predominantly neurological involvement, stenosis, lumbar tumors, osteomyelitis, systemic infection, infection of soft tissue adjacent to the spine, trauma, or moderate to severe osteoporosis. Other exclusions included reviews, editorials, case reports, and non-English language studies (Figure 1).

Data Extraction

Each retrieved citation was reviewed by two independently working reviewers (J.R.D. and R.H.). Some articles were excluded on the basis of information provided by the title or abstract if they clearly were not appropriate. Citations that appeared to be appropriate or those that could not be excluded unequivocally from the title and abstract were identified, and the corresponding full text was reviewed by the two reviewers. Any disagreement between them was resolved by consensus. From the included articles, the following data were extracted for both the surgical fusion and conservatively managed groups: diagnostic subgroup, demographics, patient characteristics, intervention details, and inclusion and exclusion criteria (Table 1); outcomes, risks of outcome (where appropriate), and pre- and postoperative and change scores for continuous measures (*i.e.*, difference between baseline and follow-up scores) (see Table 2, Supplemental Digital Content 1, http://links.lww.com/BRS/A550).

Study Quality

Level-of-evidence ratings were assigned to each article independently by two reviewers (R.H. and J.R.D.) using criteria set by *The Journal of Bone and Joint Surgery, American Volume*,[24] for therapeutic studies and modified to delineate criteria associated with methodological quality and described elsewhere (see Supplemental Digital Content 1, http://links.lww.com/BRS/A550).

Study Component	Inclusion	Exclusion
Participants	• Adults with CLBP with or without isthmic spondylolisthesis	• Patients <18 years of age • LBP with predominantly neurological involvement • Spinal stenosis • Tumor • Moderate to severe osteoporosis • Trauma • Osteomyelitis • Infection of soft tissue adjacent to spine • Systemic infection
Intervention	• Fusion with or without instrumentation or decompression	• Surgical procedures other than spinal fusion (± decompression) due to CLBP
Comparators	• Supervised rehabilitation	• Other lumbar surgeries • Non multidimensional supervised rehabilitation
Outcomes	• Physical function • Pain (VAS back and leg) • Health related quality of life • Patient satisfaction	• Nonclinical outcomes
Study Design	• Randomized controlled trials	• Nonrandomized controlled trials • Reviews • Editorials • Studies not written in English

Figure 1. Inclusion and exclusion criteria. CLBP indicates chronic low back pain; LBP, low back pain; VAS, visual analog scale.

TABLE 1. Demographics of Studies Comparing Fusion With Multidimensional Supervised Rehabilitation in CLBP Patients With and Without Isthmic Spondylolisthesis

Author (yr)	Study Design (LoE)	Follow-up (% Followed up)	Demographics	Patient Characteristics	Interventions	Inclusion/Exclusion
Patients with CLBP without isthmic spondylolisthesis						
Brox *et al*[19] (2003)	RCT Multicenter	1 yr (97%)	Fusion n = 37 Male: 43% Mean age: 44.1 ± 8.1 yr Nonoperative n = 27 Male: 33% Mean age: 42.4 ± 7.8 yr	• CLBP* • Previous spinal surgery: 0% (see exclusion criteria) • Mean pain duration Surgery: 9.6 ± 8.7 yr No surgery: 12.5 ± 11.6 yr • Any leg pain: yes,% unknown • On sick leave Surgery: 30% No surgery: 26%	Fusion (n = 37) • PLF with transpedicular screws and autologous bone at L4–L5 and/or L5–S1 • Postoperative rehabilitation: standardized advice given for first 3 mo; otherwise, postoperative rehabilitation was the surgeon's choice and not standardized Nonoperative treatment (n = 27) • Cognitive therapy + exercises as well as education and encouragement to engage in normal activities and "not be too cautious" • Physical exercises aimed to increase endurance and coordination • Supervised for 1 wk in facility, then 2 wk at home, then 2 wk in facility	*Inclusion* • CLBP • Evidence of degeneration on plain radiograph at L4–L5 and/or L5–S1 (spondylosis) • Aged 25–60 yr • Pain duration ≥ 1 yr • Oswestry Disability Index score ≥ 30 Exclusion • Previous spinal surgery • Recurrent disc herniation or lateral stenosis with clinical signs of radiculopathy • Widespread myofascial pain • Spinal stenosis accompanied by decreased walking distance and neurological signs • Inflammatory disease • Previous spinal fracture • Pelvic pain • Evidence of generalized disc degeneration on plain radiograph • Ongoing somatic or psychiatric illness • Registered medical abuse • Reluctance to accept either treatment in the study
Fairbank *et al*[20] (2005)	RCT Multicenter MRC Spine Stabilization Trial	2 yr (81%)	Fusion n = 176 Male: 45% Mean age: NR Nonoperative n = 173 Male: 54% Mean age: NR	• Spondylolisthesis†: Surgery: 11% (20/176) Rehabilitation: 10% (18/173) • Postlaminectomy: Surgery: 8% (14/176) Rehabilitation: 8% (14/173) • Mean LBP duration Surgery: 8 yr (1–35) Rehabilitation: 8 yr (1–35) • Any leg pain: yes,% unknown • On sick leave: Surgery: 40% Rehabilitation: 46%	Fusion (n = 176) • Fusion: 85% (149/176) • Flexible stabilization (Graf technique): 15% (27/176) • Fusion technique left to the discretion of the operating surgeon (including surgical approach, implant, if any, interbody cages, and bone graft material; NR) • Postoperative rehabilitation: NR Nonoperative treatment (n = 173) • Intensive rehabilitation program of education and exercise running on 5 d/wk for 3 wk	Inclusion • Chronic (>12 mo) LBP with or without referred pain • Candidate for fusion • Clinician and patient uncertain as to which of the study treatment strategies will be best • Aged 18–55 yr • No restriction on previous root decompression or discectomy Exclusion • Previous spinal fusion surgery • Ineligible for any of the trial interventions, including, but not limited to: Infection Other comorbidities (inflammatory disease, tumors, fractures) Psychiatric disease Inability or unwillingness to complete the trial questionnaires • Pregnancy

(*Continued*)

TABLE 1. (*Continued*)

Author (yr)	Study Design (LoE)	Follow-up (% Followed up)	Demographics	Patient Characteristics	Interventions	Inclusion/Exclusion
Fritzell *et al*[21] (2001)	RCT Multicenter Swedish Lumbar Spine Study	2 yr (98%)	Fusion n = 222 Male: 50% Mean age: 43 yr (25–64) Nonoperative treatment n = 72 Male: 49% Mean age: 44 yr (26–63)	• Spondylolisthesis: 0% (see exclusion criteria) • Previous spinal surgery (removal of herniated disc only, see exclusion criteria): Surgery: 18.6% Nonsurgical: 19.4% • Mean pain duration Surgery: 7.8 yr (2–34) Nonsurgical: 8.5 yr (2–40) • Any leg pain: yes,% unknown • On sick leave [mean length of time] Surgery: 59% [3.2 yr (0.1–18)] Nonsurgical: 54% [2.9 yr (0.1–8)]	Fusion (n = 222) • PLF using autologous bone: 33% (73/222) • PLF + internal fixation device [VSP with pedicle screws and plates (DePuy Acromed, Raynham, MA)]: 33% (74/222) • PLF + VSP (as earlier) + interbody bone graft (ALIF or PLIF) (surgeon preference): 34% (75/222) • All surgical patients wore a brace (PLF only group) or corset for 5 mo postoperatively • Surgical technique was assigned by randomization • Only L4–L5 and/or L5–S1 fused Nonoperative treatment (n = 72) • Physical therapy supplemented with other types of care, such as TENS, acupuncture, injections for pain relief, cognitive and functional therapy, education, and coping strategies. • Length/structure of rehabilitation: NR	Inclusion • Severe chronic (≥2 yr) LBP • Back pain greater than leg pain • Aged 25–65 yr • No signs of nerve root compression (herniated discs were acceptable) • Surgeon's diagnosis from history, physical examination, and radiography that pain emanates from L4–L5 and/or L5–S1 • Evidence of degenerative changes at L4–L5 and/or L5–S1 as visualized by plain radiographs, computed tomography, and/or MRI • Patient on sick leave or disability for ≥1 yr • Nonsurgical treatments unsuccessful • Score of ≥7/10 on the Function-Working Disability Score‡ Exclusion • Ongoing psychiatric illness • Previous spine surgery *except* successful removal of herniated disc ≥2 yr before enrollment and no persistent nerve root symptoms • Radiologic findings including spondylolisthesis, new or old fractures, infection, inflammation, or neoplasm • Painful and disabling arthritis in the hip(s) • Anamnestic and radiologic signs of spinal stenosis
Patients with CLBP with isthmic spondylolisthesis						
Möller and Hedlund[22] (2000)/ Ekman *et al*[23] (2005)	RCT	1 yr (96%) 2 yr (93%) 9 yr (91%)	All N = 111 Male: 51% Mean age: 26 yr Fusion n = 77 Male: 49% Mean age: 39 yr Nonoperative n = 34 Male: 56% Mean age: 37 yr	• Isthmic spondylolisthesis: 100% • Previous spine surgery: 0% (see exclusion criteria) • Mean pain duration: ≥1 yr • Any leg pain: Surgery: 73% Exercise: 61% • On sick leave/disability: Surgery: 75% Exercise: 62%	Fusion (n = 77) • PLF *in situ* with autologous bone transplantation harvested from the right iliac crest; without instrumentation (n = 40) and with rigid pedicle screw fixation (n = 37) • Noninstrumented patients wore a daytime brace for 6 mo after surgery • No postoperative exercise or physiotherapy program was given Nonoperative (n = 34)	Included • Lumbar isthmic spondylolisthesis of any grade • ≥1 yr of LBP or sciatica • Severely restricted functional ability • Age 18–55 yr Excluded • Mild symptoms • Previous spine surgery • Alcohol/drug abuse

(*Continued*)

TABLE 1. *(Continued)*

Author (yr)	Study Design (LoE)	Follow-up (% Followed up)	Demographics	Patient Characteristics	Interventions	Inclusion/Exclusion
					• Exercise program based on strength and postural training; overseen by a physiotherapist with special interest in spondylolisthesis • Patients exercised 3x wk the first 6 mo, and 2x wk between 6 and 12 mo (duration approximately 45 min); after 1 yr patients were instructed to continue with a home program consisting of the 8 exercises that did not require special equipment	

*Spondylolisthesis not mentioned in the article.

†Not stratified by degenerative or isthmic. Because >15% of patients (10.9%) had spondylolisthesis we considered this to be an article primarily on patients without spondylolisthesis.

‡Function-Working Disability Score: questionnaire that evaluates ability of patient to function and work; the function and working ability categories each have five items. Possible scores range from 2–10: 2 indicating "no pain, can do anything, even sports; no restrictions in working ability;" 10 indicating "severe pain, no function; completely disabled, no working ability."

ALIF indicates anterior lumbar interbody fusion; CLBP, chronic low back pain; LBP, low back pain; MRI, magnetic resonance imaging; PLF, posterolateral fusion; PLIF, posterior lumbar interbody fusion; RCT, randomized controlled trial; TENS, transcutaneous electrical nerve stimulation; VSP, variable screw placement; MRC, Medical Research Council; LoE, level of evidence; NR, not reported.

Analysis

We performed all analyses on a study level. The focus of the analysis was to evaluate subgroups within larger comparative trials. Outcome measures are reported on the basis of the authors' choice of measure(s) for treatment effects. We only included results when similar outcomes were recorded in both subgroups (*e.g.*, if a quality of life measure was assessed in studies that contained patients without spondylolisthesis but not in studies having patients with spondylolisthesis, the results of that outcome measure could not be compared). Data were not pooled because of potentially important differences in patient populations among studies. In continuous measures where a lower number represented improvement, we multiplied the outcome scores by −1 to ensure that positive scores indicated improvement. If the author reported pre- and postoperative scores and standard deviations for a particular continuous outcome measure, we calculated the change scores and corresponding standard deviations. The standardized mean differences (SMDs) comparing fusion *versus* multidimensional supervised rehabilitation were calculated by subtracting the mean change scores and dividing by the postoperative score standard deviations. If the authors reported rates (or raw count data) for particular binary outcomes, we calculated risk differences (RDs) and 95% confidence intervals (CIs) using Stata 9.0 (StataCorp LP, College Station, TX).[25] The SMDs and RDs are considered standardized effect estimates. The reporting of effect estimates facilitates the interpretation of the size of the effect of a specific treatment as opposed to the statistical significance. We qualitatively compared effect estimates visually with forest plots where appropriate to evaluate whether there was any HTE (*i.e.*, that a treatment worked better in one subgroup compared with the other).

Overall Strength of Body of Literature

The initial strength of the overall body of evidence was considered "high" if the majority of the studies were level I or II and "low" if the majority of the studies were level III or IV. We downgraded the body of evidence one or two levels on the basis of the following criteria: (1) inconsistency of results, (2) indirectness of evidence, (3) imprecision of the effect estimates (*e.g.*, wide CIs), or (4) non–*a priori* statement of subgroup analyses. We upgraded the body of evidence one or two levels on the basis of the following criteria: (1) large magnitude of effect or (2) dose-response gradient. The final overall strength of the body of literature expresses our confidence in the estimate of effect and the impact that further research may have on the results. An overall strength of "high" means we have high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. The overall strength of "moderate" means we have moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. A grade of "low" means we have low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and likely to change the

TABLE 2. Rating of Overall Strength of Evidence

Subgroups	Strength of Evidence	Conclusions/Comments	Baseline	Upgrade (Levels)	Downgrade (Levels)
Question 1: Does the presence of isthmic spondylolisthesis modify the effect of treatment (fusion or multidimensional supervised rehabilitation) in patients with CLBP?					
Isthmic spondylolisthesis	Low	The presence of isthmic spondylolisthesis in patients with CLBP may positively modify the treatment effect of fusion *vs.* multidimensional supervised rehabilitation with respect to pain and function. No apparent effect modification was noted in patient perceived improvement or willingness to repeat treatment.	High	Size of treatment effect (2)	Consistency (1) Indirect evidence (2) Non–*a priori* (1)

Baseline quality: High = majority of articles level I/II; Low = majority of articles level III/IV.

Upgrade: Large magnitude of effect (1 or 2 levels); dose-response gradient (1 level).

Downgrade: Inconsistency of results (1 or 2 levels); indirectness of evidence (1 or 2 levels); imprecision of effect estimates (1 or 2 levels).

CLBP indicates chronic low back pain.

estimate. Finally, a grade of "insufficient" means that evidence either is unavailable or does not permit a conclusion. A more detailed description of this process can be found in the Methods section of article.[26]

RESULTS

Study Selection

We identified 228 total citations from our electronic search strategy. Of these, 212 were excluded by title/abstract and 16 full text articles were evaluated to determine if they met the inclusion criteria. From these 16 studies, 12 were excluded on the following reasons: eight included patients with symptoms of spinal stenosis, one included only patients who had a prior surgery, one had both subgroups but did not present results by subgroup, one compared fusion with laminectomy or discectomy, and one had no multidimensional supervised rehabilitation as a control. The remaining four RCTs met our inclusion criteria and are summarized in this report (Figure 2). Details with respect to the articles excluded and the critical appraisal summary for included articles can be found in the supplementary tables (see Table 3, Supplemental Digital Content 1, http://links.lww.com/BRS/A550)

Study Characteristics

We found no studies meeting our inclusion criteria that compared the two subgroups of patients (those with and without isthmic spondylolisthesis); therefore, we assessed studies that compared fusion with multidimensional supervised rehabilitation in patients with or without isthmic spondylolisthesis. To this end, three RCTs were identified that compared fusion with multidimensional supervised rehabilitation in CLBP patients without isthmic spondylolisthesis[19–21] and one RCT was found that evaluated these treatments in CLBP patients with isthmic spondylolisthesis.[22] These four studies varied in patient characteristics, type of fusion and multidimensional supervised rehabilitation, outcomes assessed, and in length of follow-up (Table 1). In Fairbank *et al*,[20] at baseline, 8% of the patients had received previous lumbar surgery, 11% had spondylolisthesis (degenerative or isthmic, not stated), an unknown proportion had leg pain, and 43% were on sick leave. Because only 11% of patients had an unspecified type of spondylolisthesis, we considered this to be a study primarily on patients without spondylolisthesis. In Fritzell *et al*,[21] 18% of patients had undergone previous lumbar surgery, none had spondylolisthesis, an unknown proportion had leg pain, and 57% were on sick leave. In Brox *et al*,[19] no patient had prior surgery, an unknown proportion had leg pain, and 28% were on sick leave. There was no mention of spondylolisthesis in this study. These three studies can be compared with Möller and Hedlund study,[22] in which all of the patients had isthmic spondylolisthesis: none had undergone prior surgery, 67% reported leg pain, and 69% were on sick leave. There were also differences in the types of fusion and the control treatments used across studies. Fairbank *et al*[20] used an unspecified variety of fusion techniques (the details of which were left to the discretion of the operating surgeon) while Fritzell *et al*[21] randomly assigned a third of the patients to receive PLF, PLF plus variable screw placement, or PLF plus variable screw

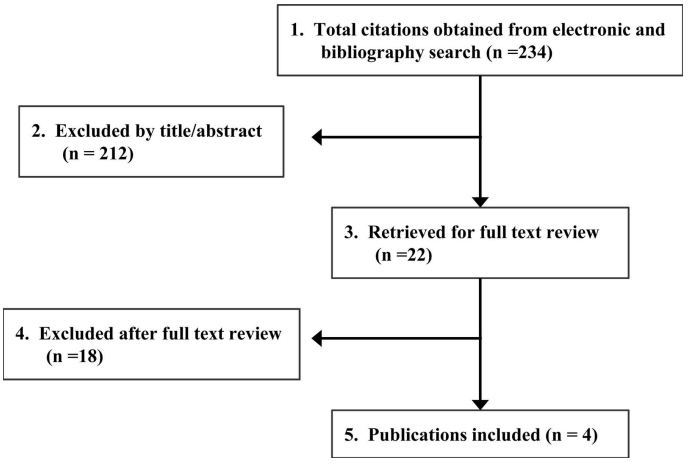

Figure 2. Flow chart showing results of literature search.

placement plus interbody bone graft (either anterior or posterior lumbar interbody fusion). Brox *et al*[19] exclusively used PLF with pedicle screws. Möller and Hedlund[22] treated the patients with isthmic spondylolisthesis with PLF with (52%) or without (48%) instrumentation. Although all studies used multidimensional supervised rehabilitation, the details varied by study. Treatments included the following: cognitive therapy, exercise, education, encouraging patients to engage in normal activities, transcutaneous electrical nerve stimulation, acupuncture, and injections for pain relief (see Table 1 for details).

Pain

Pain was reported by two[19,21] of the three studies on patients without isthmic spondylolisthesis and one[22] study on patients with isthmic spondylolisthesis. The former study[19,21] reported back and leg pain separately; both studies had patients score the intensity of their back and lower limb pain on vertical visual analog scales scores that ranged from 0 to 100. Maximum pain, minimum pain, and current pain were scored on three different scales, and the mean of the three measurements provided the pain index for back pain and lower limb pain, respectively. In the study on patients with isthmic spondylolisthesis,[22] an overall pain index was reported and did not distinguish between back and leg pain. The pain index was calculated by taking the mean of the visual analog scale scores for "pain right now" and that for "worst pain last week." The SMDs for pain in favor of fusion were modest among those without isthmic spondylolisthesis as reported by Brox *et al*[19] at 1 year and Fritzell *et al*[21] at 2 years for back pain: 0.29 (95% CI = -0.22, 0.80) and 0.70 (95% CI = 0.41, 0.99); and leg pain: 0.63 (95% CI = 0.11, 1.15) and 0.50 (95% CI = 0.21, 0.80), respectively. In contrast, there was a large effect in favor of fusion for isthmic spondylolisthesis patients as reported by Möller and Hedlund[22] at 2 years, SMD: 2.31 (95% CI = 1.79, 2.84) (Figure 3).

Function

Function was assessed in all four studies. All three studies[19–21] on patients without isthmic spondylolisthesis evaluated function using the Oswestry Disability Index; two of these three studies[19,21] also utilized the General Function Score. The study on patients with isthmic spondylolisthesis measured function using the Disability Rating Index.[22] In patients without isthmic spondylolisthesis, the SMDs for function as measured by both the Oswestry Disability Index and the General Function Score were relatively small and in favor of fusion: Oswestry Disability Index SMDs = 0.13 (95% CI = −0.38, 0.64) at 1 year, 0.18 (95% CI = −0.05, 0.42) at 2 years and 0.50 (95% CI = 0.30, 0.88) at 2 years as reported by Brox *et al*,[19] Fairbank *et al*,[20] and Fritzell *et al*,[21] respectively; General Function Score SMDs = 0.25 (95% CI = −0.27, 0.75) at 1 year and 0.59 (95% CI = 0.30, 0.88) at 2 years for Brox *et al*[19] and Fritzell *et al*,[21] respectively. In contrast, the SMD for function as measured by the Disability Rating Index was appreciably higher in favor of fusion in patients with isthmic spondylolisthesis as reported by Möller and Hedlund[22] at 2 years: SMD = 3.03 (95% CI = 2.45, 3.62) (Figure 3).

Patient Improvement Rating

Two studies reported whether patients were improved ("better" or "much better") as assessed by patient perception and whether patients were willing to go through the treatment again. In both studies, the proportion of patients that reported improvement was higher in the fusion group than in the multidimensional supervised rehabilitation group. However, the proportions favoring fusion were similar at 2 years

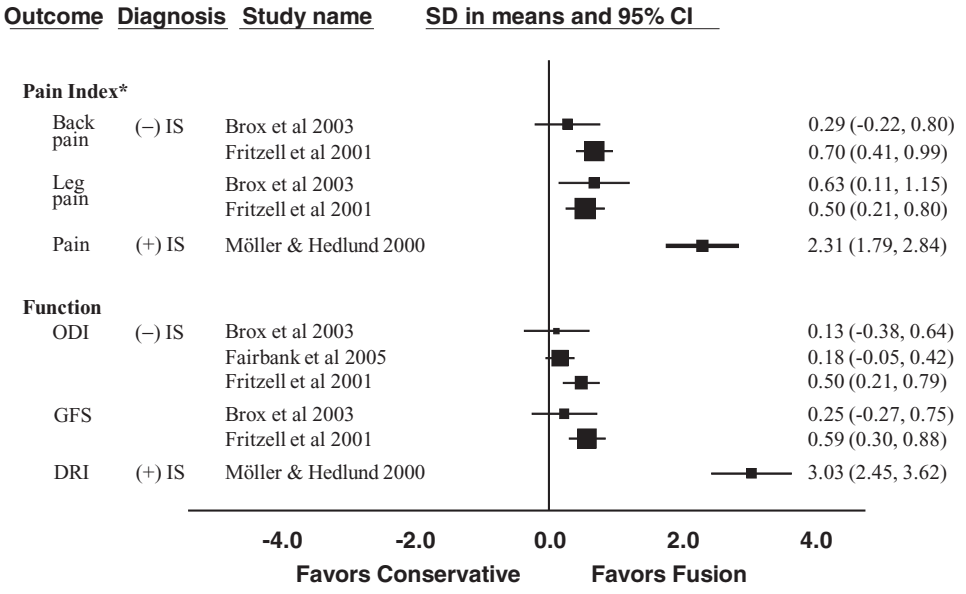

Figure 3. Standardized mean differences of pain and function outcomes comparing those without and with IS. CI indicates confidence interval; DRI, Disability Rating Index; GFS, General Function Scale; IS, isthmic spondylolisthesis; ODI, Oswestry Disability Index; VAS, visual analog scale.

*Brox et al and Fritzell et al assessed back and leg pain separately using the mean of 3 VAS parameters maximum pain, minimum pain, and current pain; Moller and Hedlund report pain using the mean of 2 VAS parameters: pain right now and worst pain last week, irrespective of location of pain.

comparing groups without[21] and with[22] isthmic spondylolisthesis, with the following RDs: 34% (95% CI = 21%, 48%) compared with 33% (95% CI = 13%, 53%), as reported by Fritzell *et al*[21] and Möller and Hedlund,[22] respectively (Figure 4). In addition, a slightly higher proportion of patients without[21] isthmic spondylolisthesis receiving fusion reported a willingness to go through the same treatment again compared with patients with[22] isthmic spondylolisthesis, RDs = 22% (95% CI = 8%, 37%) compared with 11% (95% CI = −8%, 30%), as reported by Fritzell *et al*[21] and Möller and Hedlund[22] at 2 years, respectively (Figure 4).

Complications

The complication rates reported by the studies varied considerably and, given the small number of studies cited, whether they are truly clinically significant remains uncertain. The study by Fritzell *et al*[21] as well as that by Brox *et al*[19] both reported an 18% complication rate, whereas that of Fairbank *et al*[20] was 11%. These included wound infections, dural tears, vascular injuries (anterior approaches), excessive bleeding, implant problems, thrombosis, and iatrogenic lumbar radiculopathies. The study by Möller and Hedlund[22] of patients with isthmic spondylolisthesis, only described three complications in 77 patients (4%), although they were serious; two permanent nerve root injuries and one patient with permanent blindness.

Evidence Summary

The overall strength of evidence evaluating whether the presence of isthmic spondylolisthesis modifies the effect of fusion compared with comprehensive rehabilitation in patients with CLBP is "low." A low strength of evidence suggests that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. (Table 2)

DISCUSSION

The purpose of this systematic review was to determine whether the presence of isthmic spondylolisthesis modifies the effect of treatment (fusion *vs*. comprehensive rehabilitation) in patients with CLBP. We initially sought studies that had subgroup analyses reporting results of statistical interaction. Finding no such study, we qualitatively compared effect estimates visually with forest plots to determine if fusion or comprehensive rehabilitation was more effective in one subgroup compared with the other. With respect to pain and function, the SMD favored fusion and was much greater in those with isthmic spondylolisthesis compared with those without. In contrast, there was no difference in the effect sizes for patient improvement rating as measured by patient-perceived improvement and willingness to undergo treatment again in those with and without isthmic spondylolisthesis.

Although we were able to perform a thorough literature review and included RCTs for analysis, our conclusions are compromised somewhat due to the variability in patient populations and treatments in the articles studied. For example, in the studies of CLBP without isthmic spondylolisthesis, Fairbank *et al*[20] included some patients with spondylolisthesis or pain after previous laminectomy while Brox *et al*[19] and Fritzell *et al*[21] did not. Fifteen percent of the fusion patients in Fairbank *et al*[20] were treated with a flexible stabilization procedure (Graf technique), whereas the other 85% had a procedure that was left to the discretion of the operating surgeon, including approach, implants, interbody cages, or bone graft material. Fritzell *et al*[21] had three fusion arms that included PLF using autograft, PLF plus an internal fixation device with pedicle screws and plates, and PLF with internal fixation plus interbody bone graft (either anterior or posterior lumbar interbody fusion), whereas Brox *et al*[19] provided PLF with transpedicular screws in all his patients. Nonoperative treatment varied among the studies as well, for although all studies included it, there were varying degrees and depth of cognitive treatment and education described. In addition, the structure and length of rehabilitation differed among the studies.

The study by Möller and Hedlund[22] that included CLBP with isthmic spondylolisthesis included listhesis of any grade and did not review the results according to the degree of slippage. As well, half of those treated with a fusion were fixed with pedicle screw instrumentation, while the other half was simply fused *in situ* without fixation. Nonetheless, the Möller and Hedlund[22] study appears to confirm the impressions of earlier authors that fusion improves pain and function better than multidimensional supervised rehabilitation in the subgroup of CLBP patients with isthmic spondylolisthesis. It, clearly, is important to remember, however, that this is but one single relatively small RCT, and although there appears a relatively strong treatment effect, their results should still be

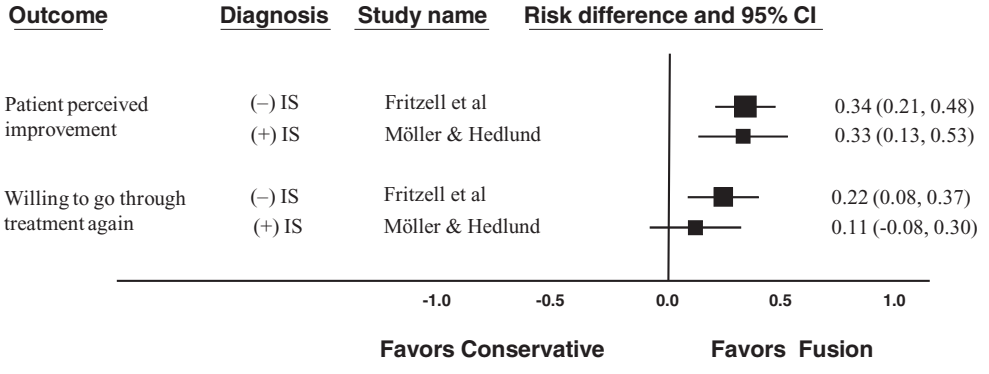

Figure 4. Risk differences of patient perceived improvement and patient's willingness to go through treatment again comparing those without and with IS. CI indicates confidence interval; IS, isthmic spondylolisthesis.

interpreted with some caution. Interestingly, however, it appears that from a patient improvement and satisfaction perspective, the percentage favoring fusion was similar between the groups with and without isthmic spondylolisthesis, both of which were higher than those reported that they had undergone rehabilitation therapy.

Trying to arrive at firm conclusions is also difficult, given the limitations of indirect comparison as we were forced to do, by failing to study any published research that compared the two subgroups (those with isthmic spondylolisthesis and those without). Certainly, future research would be aided by somehow designing studies that either directly compare the two groups with each other, or having equal representations of the two compared with an organized rehabilitation program.

A recent publication by Ohtori *et al*[27] summarized a small-sized RCT comparing surgical *versus* nonsurgical care for selected patients with discogenic LBP. Their comparison focused on patients with LBP (without spondylolisthesis) for at least 2 years and was limited to one level at the lower lumbar region without radiculopathy. In their comparison of 21 patients treated surgically *versus* 20 performing exercises, they found a strong treatment effect in favor of surgical intervention at both 1- and 2-year follow-up. This report was not included in our analysis for the following reasons: (*a*) Of 98 eligible patients, 46 were excluded for unwillingness to undergo preoperative discographic examination; and (*b*) another 11 patients were later excluded for having mixed results on the discogram. Thus, 57 of 98 (58%) of patients who would otherwise have been eligible in the studies analyzed in this report were excluded. Discography has drawn increasing scrutiny of late as both a diagnostic as well as predictive test for the surgical treatment of degenerative LBP.[28,29] In addition, in their study, the nonoperative arm consisted of only unsupervised daily walking and 30 minutes of stretching per day. For these reasons, although the apparent treatment effect is substantial, we did not feel that it merited comparison with the articles included here.

Why the results when treating patients with CLBP and isthmic spondylolisthesis may be superior to those of patients with CLBP without the defect remains somewhat uncertain. Of the four articles cited here, the complication rate was evidently much lower in the group with isthmic spondylolisthesis; however, given the small number of studies involved, and the lack of side by side comparison, it remains somewhat difficult to expect that these outcomes would be repeated in other instances. It may be that there is an element of relative instability that is present in spondylolisthesis that is absent in those with discogenic degeneration and this may respond more favorably to surgical stabilization. The chronic defect of the pars interarticularis may also be a source of pain not seen in the other population that also responds well to fusion. Finally, it may also well be that the outcomes from the operative treatment of patients with CLBP without isthmic spondylolisthesis may be more variable and statistically difficult as, to date, the true source of pain in those with degeneration of the intervertebral disc remains somewhat more elusive than that of the more easily definable mechanics of isthmic spondylolisthesis. All of these considerations, however, require much investigation and research at both the clinical and basic science levels before drawing firm conclusions.

Nonetheless, on the basis of our well-defined review of the available literature, it does appear that patients with CLBP and isthmic spondylolisthesis, as compared with those without, can be treated differently when considering care, especially surgery: They are different and they respond differently.

➢ Key Points

- ❑ Three RCTs compared fusion with multidimensional supervised rehabilitation in patients with CLBP without isthmic spondylolisthesis and one RCT evaluated these treatments in patients with isthmic spondylolisthesis.
- ❑ There were study differences in patient characteristics, type of fusion, the nature of the rehabilitation, outcomes assessed, and length of follow-up.
- ❑ The SMDs for pain and function in favor of fusion were modest at 2 years among those without isthmic spondylolisthesis, but large in favor of fusion among those with isthmic spondylolisthesis compared with rehabilitation.
- ❑ Fusion should be considered for patients with LBP and isthmic spondylolisthesis who have failed nonoperative treatment.

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