Transport Accident Commission & WorkSafe Victoria

Evidence Service

Lumbar Spinal Fusion

Evidence Review

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A joint initiative of

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BACKGROUND

Patient group

Chronic low back pain (CLBP) is characterised by pain persisting for longer than three months.[1] Some common theories as to the sources of CLBP include:[1]

Herniated discs: where the outer part of the disc bulges out into the spinal canal.

Degenerative disc disease: where the discs flatten and dry out.

Isthmic spondylolisthesis: where the lowest lumbar vertebrae slips forward as a result of a stress fracture in childhood.

Degenerative spondylolisthesis: where the lowest lumbar vertebrae slips forward as a result of degenerative changes.

Lumbar spinal stenosis: when there is spinal degeneration causing the spinal canal to narrow compressing the spinal cord and nerves.

Lumbar spondylosis: where there is general degeneration of the lumbar spine, particularly the small joints (i.e. degenerative changes at L4-L5 and/or L5-S1).[3]

Spinal fusion

The aim of surgical fusion is to reduce pain and decrease disability associated with the above conditions. The rationale for spinal fusion is that pain arises from a degenerative motion segment and consequently, fusion surgery helps eliminate excessive motion and its subsequent pain.[2] There are two main types of lumbar spinal fusion, which may be used in conjunction with each other:[4]

- Posterolateral fusion: places a bone graft to form a bony bridge between the transverse processes in the back of the spine. These vertebrae are then fixed in place with screws and/or wire through the pedicles of each vertebra attaching to a metal rod, plate or cage on each side of the vertebrae (often called 'fixation').
- Interbody fusion: places a bone graft between the vertebrae in the area usually occupied by the intervertebral disc. In this instance, the disc is completely removed and replaced with a graft. This will allow the fusion to occur from one vertebral body to the other through their endplates. The surgical incision for interbody fusion will be either anterior, posterior or transforaminal.

The indication for spinal fusion surgery and how it should be performed for the relief of ongoing symptomatology however, remains unclear or controversial.[2]

Non-surgical treatments

The management of CLBP conditions and their symptoms remains controversial, with a variety of surgical and non-surgical treatment options available.[2] The traditional non-surgical approach may include a series of rehabilitative physiotherapy techniques in isolation or in combination with, epidural steroid injections, non-steroid anti-inflammatory drugs or opioid administration.[4] Other therapies also include a series of structured clinical programs that provide intensive multidisciplinary rehabilitation encompassing a series of physical, psychological, social and occupational patient factors.[5-7]

Regulatory status

Spinal fusion surgery is listed under the Medicare Benefits Schedule (MBS) as a *Category 3 Therapeutic Procedure* and is covered by the following item numbers:

- fusion to cervical, thoracic or lumbar regions (48660-48675)
- fusion, posterior (40321,40324,40327)
- fusion, posterior interbody, with laminectomy (48654,48657)
- using segmental instrumentation (48613)

There have been no submissions to the Medical Services Advisory Committee (MSAC) or guidance from the Food and Drug Administration (FDA) in the United States regarding the safety, effectiveness, and cost considerations associated with spinal fusion surgery for the treatment of degenerative conditions of the spine that have failed to respond to conservative treatment.

Intended purpose of the review

The Transport Accident Commission (TAC) and WorkSafe Victoria (WSV) requested a review of the evidence to determine whether spinal fusion is an effective treatment compared to non-surgical treatment in patients with CLBP. This report sought to answer the following questions:

1. What is the effectiveness of spinal fusion on persistent pain?
2. What is the effectiveness of spinal fusion on function, quality of life, return to work and medication use?
3. What are the potential harms or risks of spinal fusion?
4. In what conditions is spinal fusion indicated, and are there any reliable diagnostic procedures that predict the success of a fusion operation?

METHODS

Methods are outlined briefly below. More detailed information about the methodology used to produce this report is available in Appendices 1 and 2. All appendices are located in the Technical Report accompanying this document.

Stage 1: Identify relevant research

A comprehensive search of Medline, PreMedline, EMBASE, CINAHL, the Cochrane Database of Systematic Reviews, DARE, CENTRAL, NHSEED, HTA and ACP Journal Club, and Web of Knowledge was undertaken in November 2012 to identify relevant synthesised research (i.e. evidence-based guidelines (EBGs), systematic reviews (SRs), health technology assessments (HTAs)) published from 1992 onwards. An additional search was conducted to identify any relevant randomised controlled trials (RCTs). A comprehensive search of the internet, relevant websites and electronic health databases was also undertaken (see Appendix 2, Tables A2.2-A2.4 for search details). Reference lists of included studies were also scanned to identify relevant references.

Studies identified by the searches were screened for inclusion using specific selection criteria (see Appendix 2, Table A2.1). Synthesised evidence (EBGs, SRs and HTAs) that met the selection criteria were reviewed to identify the most up-to-date and comprehensive source of evidence, which was then critically appraised to determine whether it was of high quality. This process was repeated for additional sources of evidence, if necessary, until the most recent, comprehensive and high quality source of evidence was identified for each indication. All screening and selection was conducted independently by two reviewers, results were compared and any discrepancies discussed and resolved. Findings from the best available source of evidence were compared to other evidence sources for consistency of included references and findings.

Stage 2: Address further actions identified

See algorithm in Table 1.

Table 1. Further action required to answer clinical questions.

<table>
<tr><th colspan="5">Is there any synthesised research available? (e.g. EBGs, HTAs, SRs)</th></tr>
<tr><th colspan="3">Yes</th><th colspan="2">No</th></tr>
<tr><th colspan="3">Is this good quality research?</th><th colspan="2">Are RCTs available?</th></tr>
<tr><th colspan="2">Yes</th><th>No</th><th>Yes</th><th>No</th></tr>
<tr><th colspan="2">Is it current (within 2 years)?</th><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>No further action</td><td>Update existing SR</td><td>Undertake new SR and/or meta-analysis</td><td>Undertake new SR and/or meta-analysis</td><td>Consider looking for lower levels of evidence</td></tr>
</table>

For each indication, the most recent, relevant, high quality piece of evidence was used to address the questions posed above.

RESULTS

Database searches yielded 1,719 articles, which were screened for potential relevance. Of these, 79 articles thought to be relevant were retrieved in full text and reviewed. From this review 22 articles were selected for inclusion (9 SRs and 13 RCTs). A further 3 EBGs were identified from the results of an internet search, bringing the total number of included studies to 25.

In total, 25 papers were included, consisting of:

- 12[2, 8-18] Synthesised studies (SRs or EBGs)
- 13[3-7, 19-26] primary study references (RCTs)

The above evidence assessed the effect of spinal fusion surgery with non-surgical treatment for the following indications: CLBP with disc degeneration, CLBP with discogenic pain, isthmic spondylolisthesis and degenerative spondylolisthesis.

Chronic low back pain with disc degeneration

Study characteristics

We identified eight SRs[2, 8-10, 12-15] that evaluated the effectiveness of fusion for the treatment of chronic low back pain (CLBP) with disc degeneration. The most comprehensive of these was by Mirza (2007),[14] which included four RCTs; Brox (2003),[3] Brox (2006),[6] Fairbank (2005)[7] and Fritzell (2001)[20] comparing fusion to non-surgical treatment for chronic low back pain with disc degeneration.

Our search also identified three additional publications, that were published since Mirza (2007)[14], These publications presented either long term data or secondary analyses of studies included in Mirza (2007)[14]. These included Brox (2010)[5] which presented long-term pooled follow-up data for the Brox (2003)[3] and Brox (2006)[6] RCTs; and Keller (2004)[23] and Froholdt (2011), [21] which provided a secondary analysis on 124 patients with CLBP from Brox (2003)[3] and Brox (2006).[6]

Quality appraisal of the Mirza (2007)[14] SR found it to have a low to moderate risk of bias (see Appendix 5 Technical report).

Participants

All of the four trials from Mirza (2007)[14] included adult patients with CLBP with disc degeneration. The length of time patients had experienced CLBP varied among studies. One study included patients who had CLBP for more than two years,[20] two studies included patients who had CLBP for at least one year[3, 6] and one study included patients with CLBP for more than 12 months.[7]

Three of the trials specifically recruited patients who also had spondylosis, (degenerative changes at L4-L5 and/or L5-S1).[3, 6, 20] Two studies also required patients to have an Oswestry Disability Index (ODI) greater than 30 out of 100 points,[3,6] and one study[20] required patients to have a score of at least 7 out of 10 on the "Function and Working Disability" index.

Two studies recruited patients who had undergone previous surgery: Fairbank (2005)[7] included patients with CLBP irrespective of previous decompression or discectomy surgery, while Brox (2006)[6] specifically recruited patients who had previously undergone disc herniation surgery.

Intervention

In all four trials included in Mirza (2007)[14] the surgical intervention was fusion surgery; however the type of fusion varied. In Brox (2003)[3] and Brox (2006)[6] the type of fusion surgery was posterolateral fusion with transpedicular screws of the L4-L5 and/or L5-S1 with the use of autologous bone. The intervention in Fritzell (2001)[20] consisted of three surgical subgroups: Group 1a consisted of posterolateral fusion with a plastic brace post-surgery, Group 1b consisted of posterolateral fusion with the addition of an internal fixation device and a canvas corset post-surgery, and Group 1c consisted of surgery the same as Group 1b with an additional interbody bone graft either as an anterior lumbar interbody fusion or posterior lumbar interbody fusion, according to the preference of the surgeon. In the study by Fairbank (2005)[7] the choice of fusion was made by the operating surgeon.

Comparator

The comparator in all four trials included in Mirza (2007)[14] was non-surgical treatment. In three trials the non-surgical treatment consisted of intensive physical therapy with a cognitive and behavioral treatment program (75 hours over three weeks, with subsequent follow-up visits).[3,6,7]

In the trial by Fritzell (2001)[20] included in Mirza (2007)[14] the non-surgical treatment intervention was less intensive (70 hours of supervised physical therapy over a two-year period) and more heterogeneous (could be supplemented with other forms of treatment, such as information and education, treatments aimed at pain relief (TENS, acupuncture, injections), or cognitive and functional training and coping strategies).

Outcome

The RCTs included in Mirza (2007)[14] assessed functional outcomes such as ODI[20,3,6,7] and general function score;[3, 6, 20] pain using a visual analogue scales (VAS);[3, 6, 20] work status;[3, 6, 20] quality of life using life satisfaction; [3] complications;[3, 6, 7, 20] medication use assessed as daily defined doses using Anatomical Therapeutic Chemical Classification System codes;[3, 6] and mental health using the Medical Outcomes Study 36-Item Short Form General Health Survey (SF-36) mental component score,[7] emotional distress using the Hopkins symptom check list-25[3, 6] and Zung depression scale.[20]

Keller (2004)[23] and Froholdt (2011)[21] only assessed trunk muscle strength, cross-sectional area and density.

Follow-up

Two trials, Brox (2003)[3] and (2006),[6] measured outcomes one year after baseline assessment and two trials, Fairbank (2005)[7] and Fritzell (2001) [20] measured the final outcomes at two years.

The Brox (2010)[5] study was a four-year follow-up of patients from the Brox (2003)[3] and Brox (2006)[6] trials.

Keller (2004)[23] assessed the trunk muscle strength of patients at their one-year follow-up; these patients were again assessed by Froholdt (2004)[21] between seven and eleven years after treatment.

Study quality

One of the main issues regarding study quality was that three of the four trials included in Mirza (2007)[14] were underpowered to detect a significant difference with regards to the primary outcome.[3, 6, 7] This particularly applies to Brox (2003)[3] and (2006),[6] which reported no significant treatment effect between fusion and non-surgical treatment. Furthermore, due to the nature of surgical trials, patients and clinicians could not be reasonably blinded to treatment. Given that surgery can be associated with important placebo effects, an overestimation of subjective outcomes such as pain cannot be ruled out.

Results

Pain

Three trials reported on the mean difference (MD) from base line for lower limb and back pain using VAS.[3, 6, 20] The results for improvement in pain were inconsistent between trials. In the trial by Fritzell (2001)[20] patients randomised to surgery experienced moderately greater improvements in back pain (21.0 vs 4.3, P = 0.0002).[20] However two smaller trials, Brox (2003)[3] and (2006)[6] reported no significant difference in back pain scores from baseline, between fusion and non-surgical treatment (MD 8.6, 95%CI -3.0 to 20.1)[3] and (MD -5.2, 95%CI -18.0 to 7.6).[6]

Two trials, Fritzell (2001)[20] and Brox (2003),[3] found a significant mean difference from baseline for lower limb pain scores in favour of fusion (6.3 vs -7.0, P=0.005)[20] and (MD 17.5, 95% CI 4.3 to 30.7),[3] however the third trial, Brox (2006)[6] found no significant difference (MD -2.7, 95%CI -15.8 to 10.4).[6] At the four-year follow-up, the pooled estimate for Brox (2003)[3] and Brox (2006)[6] showed no significant difference in pain scores between fusion and non-surgical treatment for either back or lower limb pain.[5]

Functioning

Oswestry Disability Index

All four RCTs in the Mirza (2007)[14] review reported ODI as a measure of function. For Fritzell (2001),[20] Brox (2003)[3] and Fairbank (2005)[7] the change in ODI was greater in the surgical group than

the non-surgical group. In contrast, Brox (2006)[6] reported a greater change in ODI in the non-surgical group compared to the surgical group.

For the ODI, we conducted a meta-analysis (Figure 1) to determine the estimates of the mean difference in ODI by combining the separate estimates of the inverse variance-weighted log mean differences from each of the studies. The results of this revealed that the mean overall difference in ODI between the fusion and non-surgical groups was -5.10 in favour of surgery (95% CI -8.19 to -2.01, p=0.001, I2 0%). Overall the results from each of the studies were similar with no evidence of heterogeneity.

However despite the differences in ODI being significantly in favour of surgery, the changes in scores were lower than the clinically meaningful difference. For patients following lumbar spinal surgery a difference in ODI of 12.8 points or above is considered clinically meaningful.[27]

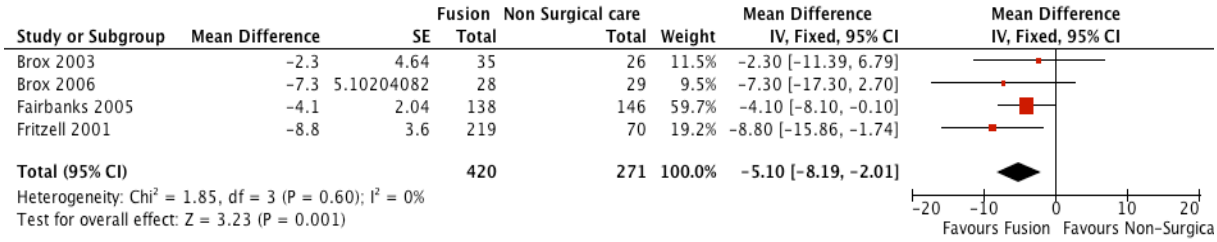

Figure 1. Meta-Analysis of ODI scores.

General function

Three trials assessed general function using a general function score.[3, 6, 20] Only Fritzell (2001)[20] found that fusion significantly improved general function compared to non-surgical treatment (MD at two years, 15 vs 2.1 P=0.005). The two smaller trials by Brox[3, 6] found no significant difference in general function scores for patients treated with fusion compared with non-surgical treatment (MD -4.1, 95%CI -14.9 to 6.7)[3] and (MD -9.5, 95%CI -20.7 to 1.6).[6] The trial by Fairbank (2005)[7] reported no significant difference in the SF-36 physical and social functioning domain between the fusion and non-surgical treatment.[7]

Quality of life

One trial, Brox (2003),[3] reported on quality of life, measuring "Life Satisfaction" as a secondary outcome. This study reported a significant improvement, from baseline, in life satisfaction scores for both the fusion and non-surgical groups, however, the difference between groups was not significant (MD 0.8, 95%CI: -2.1 to 0.5).[3]

Mental health

None of the studies found a significant difference between fusion and non-surgical treatment with regards to mental health.

Return to work

In the three trials that measured "return to work" only a small percentage of patients were working at baseline and follow-up. One study reported a significant difference in favour of fusion expressed as "net back to work" (36% fusion group vs 13% for non-surgical group p=0.002) and also as "back to work" (39% fusion group vs 23% non-surgical group p=0.049).[20] Two smaller trials found no significant difference in back to work rates between fusion and non-surgical treatment.[3, 6]

Brox (2010)[5] reported an increase in the number of patients working in both the fusion and non-surgical groups at follow-up compared to baseline, however the difference between the groups was not significant.

Medication use

Two trials examined the use of pain medication and found no difference in use between fusion and non-surgical treatment (MD -0.4, 95%CI -1.1 to 0.5[3] and MD -0.3, 95%CI -1.3 to 0.3[6]).

Muscle strength

Studies by Keller (2004)[23] and Froholdt (2011)[21] conducted secondary analyses of combined data from Brox (2003),[3] Brox (2006).[6] The objective of these studies was to investigate the differences in muscle strength, cross-sectional area, and density of the back muscles in patients with CLBP with disc degeneration randomised to either lumbar fusion or cognitive intervention and exercises.

The study by Keller (2004)[23] found that at one-year follow-up, patients treated with cognitive intervention and exercise programs improved significantly in muscle strength compared with patients who underwent lumbar fusion. This effect was lost in the longer term with an analysis at seven to eleven years post intervention showing no significant difference between fusion and non-surgical treatment.[21] The cross-sectional area remained unchanged in both treatment groups at both time points.

Complications

In the two Brox RCTs early surgical complication rates were 8%[6] and 18%[3], with no late complications reported. The study by Fritzell (2001)[20] reported that 17% of patients suffered early complications, the majority of which were handled with no obvious sequelae. Fairbank (2005)[7] reported that intra-operative complications occurred in 10% of patients; with 6% requiring further operations on their lumbar spine during the two-year follow-up. Major complications included deep wound infections, major bleeding during surgery, thrombosis, acute respiratory distress syndrome, pulmonary oedema, and heart failure.

Discussion

It is unclear whether fusion is more effective than non-surgical treatment in patients CLBP with disc degeneration. Overall the body of evidence relies on a small number of trials, some of which have relatively small sample sizes and are underpowered.

Overall the results were variable between the different trials. For example the trial by Fritzell (2001)[20] appeared to provide strong evidence in favour of fusion, but more recent studies by Brox[3,5,6] found no significant difference between treatment groups. A plausible explanation for the observed inconsistencies was the variability in the non-surgical therapies between the trials. For example the studies that used intensive physical therapy in combination with cognitive intervention[3,6,7] reported no significant difference between treatment arms, whereas in the one trial that showed fusion to be more effective,[20] the non-surgical treatment was less structured and less intensive.

The patient groups were also different between these trials with only the Fritzell (2001)[20] study enrolling patients who had previously failed non-surgical treatment. Given that this trial was the only one showing a significant improvement with fusion, it may be that fusion is effective as last-line therapy in patients with CLBP, but less effective as first- or second-line therapy.

Other issues were the high crossover rate of patients from the non-surgical treatment group to fusion and high dropout rates as reported by Fairbank (2005).[7]

Conclusion

There is insufficient evidence to determine the effect of fusion compared to non-surgical treatment in patients with CLBP with disc degeneration. Although there is limited evidence to suggest that surgery could be effective as a final therapy option when compared with unstructured non-surgical treatment, it may be equally as effective when compared to intensive rehabilitation with cognitive intervention and exercises in patients who are yet to fail non-surgical therapy. Due to the methodological limitations of the current RCTs further research is required to accurately assess the effect of fusion in CLBP patients with disc degeneration.

Discogenic low back pain

Study characteristics

We identified one RCT by Ohtori (2010)[25] examining the effectiveness of fusion for the treatment of discogenic low back pain (DLBP) without radicular (leg) pain. This study was different from those included in the "CLBP with disc degeneration" section of the report as it specifically included CLBP patients with a diagnosis of discogenic pain (i.e. disc degeneration only at 1 level (L4/5 or L5/S1) on MRI, pain provocation on discography, and pain relief by discoblock).

Forty-one discogenic/discography positive patients were randomised into three groups; a control group and two surgery groups. The two surgery groups consisted of 15 patients who received anterior interbody fusion (ABF) and six patients who received posterolateral fusion with pedicle screws (PLF). The control group consisted of 20 patients who underwent an exercise program. The exercise program consisted of daily walking (30 minutes twice a day) and muscle stretching (body and legs) (15 minutes twice a day). The walking was performed independently by the patient at

home while the muscle stretching was performed in hospital with a physiotherapist. Patients were excluded if they did not perform the walking and stretching precisely as instructed.

This study measured functional disability using the ODI, and pain using a VAS (0, no pain; 10, worst pain) and the Japanese Orthopedic Association Score (JOAS: 0 = worst pain; 3 = no pain). These outcomes were measured at baseline and one and two years after treatment. Other outcomes such as quality of life, return to work and medication use were not reported in this trial.

Results

Pain using VAS

At two years post treatment there was an improvement in self-reported end point pain scores in those receiving fusion, with significantly lower pain VAS scores and higher pain JOAS scores in the both the ABF and PLF groups compared to the exercise group.

We calculated the mean difference between the groups at two years and found that for ABF compared to non-surgical treatment, the mean difference in VAS scores was -3.4, SE 0.35 (95% CI,-4.087,-2.71) and the mean difference for PLF compared to non-surgical treatment was -2.2, SE 0.39, (95%CI, -2.96,-1.43). For pain using JOAS the mean difference between ABF and non-surgical treatment was 1.3, SE; 0.10, (95% CI, 1.1, 1.50) and for PLF compared to non-surgical treatment 0.8, SE 0.1765, (95% CI, 0.45, 1.14).

Function

There was no difference in ODI between groups at baseline. At one and two years post treatment, ODI was significantly lower in both the ABF and PLF group compared to the exercise group ($P<0.01$). We calculated the mean difference between the groups at two years and found the mean difference between ABF and non-surgical treatment to be -29.7, SE 2.30, (95%CI,-34.18, -25.21) and between PLF and non-surgical treatment (-18.8, SE 3.00, 95%CI, -24.69, -12.90).

Other outcomes

The study by Ohtori (2010)[25] did not report on quality of life, return to work, medication use or complications.

Discussion

Although the results showed a significant improvement in fusion compared with non-surgical treatment there is some uncertainty regarding the results. This study had a moderate risk of bias, its main limitation was that trial patients and clinicians could not be reasonably blinded to treatment and given that surgery can be associated with important placebo effects, an overestimation of subjective outcomes such as pain cannot be ruled out. Also the results of this study are based on a small sample of patients and given that this is the only trial investigating the effect of fusion on patients with discogenic low back pain, the generalisability of these results is unclear.

Conclusion

Given the limitations of this study and the paucity of evidence, there is insufficient evidence to confirm whether spinal fusion is as effective as non-surgical treatment in people with discogenic low back pain without radicular (leg) pain.

Isthmic spondylolisthesis

Study characteristics

We identified one RCT by Moller (2000),[24] which investigated the effect of fusion with non-surgical treatment in CLBP patients with isthmic spondylolisthesis. This study included adults aged 18-55 years with lumbar isthmic spondylolisthesis of any grade, with at least one year of low back pain or sciatica, and a severely restricted functional ability. In this study 111 patients were randomly allocated to an exercise program (n= 34) or posterolateral fusion with or without transpedicular fixation (n=77). All 77 patients who underwent surgery had a posterolateral fusion in situ with autologous bone transplantation harvested from the right iliac crest. Patients in the non-surgical treatment group underwent an intensive exercise program, developed by a physiotherapist with a special interest in spondylolisthesis. The exercise program was supervised by the physiotherapist and performed three times a week for the first six months, and twice a week between six and twelve months. Outcomes were assessed at one and two years post treatment and included pain using a 0-100 point VAS and functional disability using the Disability Rating Index (DRI). Nine year follow-up data were published by Ekman (2005).[19] Ekman (2005)[19] included an additional outcome measure, "Global Outcome", which was assessed by patients, who classified their overall results as 'much better,' 'better,' 'unchanged' or 'worse.'

Results

Pain

The surgically treated group reported a significantly lower pain index (P = 0.002, data not reported) at the two-year follow-up assessment than the exercise group. There were mean pain index improvements from baseline in both groups: 63 (range, 10–98) to 37 (range, 0–96) in the surgical group (P = 0.0001), and from 65 (range, 32–96) to 56 (range, 17–87) in the exercise group (P = 0.024). This difference was no longer significant at the nine-year follow-up assessment.

Function

The surgically treated group reported a significantly lower DRI (P =0.004, data not reported) at the two-year follow-up assessment than the exercise group. At the two-year follow-up assessment, 11 of the 12 functional scores were significantly better in the surgical group than in the exercise group. Among all 106 patients that completed the two-year follow-up assessment, surgically treated

patients accounted for 34 of the 37 patients with a DRI lower than 20, and 28 of the 29 patients with a pain index lower than 20. This difference was no longer significant at the nine-year follow-up assessment.

Global outcome

Global outcome at nine years was significantly better in the surgical group than in the exercise group. In the surgical group 76% of patients classified their result as much better or better compared with 50% in the exercise group (p = 0.015). This outcome was not reported at the two-year follow-up.

Complications

In the surgical group, three major operative complications occurred. In two of the thirty-seven patients who underwent surgery with transpedicular fixation instrumentation, an L5 root injury occurred with permanent sequelae. Dermatomal pain developed in both patients, and one experienced permanent extension weakness of the foot. One non-instrumented surgical patient became permanently blind in one eye. No complications occurred in the exercise group.

Other outcome measures

The study by Moller (2000)[24] did not report on quality of life, return to work or medication use.

Discussion

This study had a moderate risk of bias, its main limitation was that trial patients and clinicians could not be reasonably blinded to treatment and given that surgery can be associated with important placebo effects, an overestimation of subjective outcomes such as pain cannot be ruled out. Also the results of this study are based on a small sample of patients and given that this is the only trial investigating the effect of fusion on patients with isthmic spondylolisthesis, the generalisability of these results is unclear.

Conclusions

In CLBP patients with isthmic spondylolisthesis, fusion improved the pain response and functional activity more than multidimensional supervised rehabilitation at two years. However, this is a single relatively small RCT, and although there appeared to be a relatively strong treatment effect, the results should be treated with caution.

Degenerative spondylolisthesis

Study characteristics

We identified one RCT by Weinstein (2007),[4] which compared the effectiveness of surgical and non-surgical treatment among CLBP patients with degenerative spondylolisthesis. Patients were offered the option of enrolling into a randomised cohort (where patients were randomised to treatment) or an observational cohort (where patients were given the option to choose either fusion or non-surgical care). Treatment was standard decompressive laminectomy (with or without fusion). Non-surgical treatment included any of the following: active physical therapy, education or counseling, instructions for exercising at home, and non-steroidal anti-inflammatory agents if tolerated. Throughout the trial, patients in the observational cohort and the non-surgical treatment groups had the option of crossing over to surgery. Both the randomised and observational cohorts were followed up for two years. The primary outcome measures were the SF-36 bodily pain and physical function domains and the modified ODI.

This study compared surgical and non-surgical treatments at six weeks, three months, six months, one year, and two years using changes from baseline for SF-36 bodily pain and physical function and for the ODI. The randomised cohort was analysed on an intention-to-treat basis, however due to the high rate of crossover, an as-treated analysis was also performed.

Results

The authors enrolled 304 patients in the randomised cohort and 303 in the observational cohort. In both cohorts, >95% of patients underwent decompressive surgery with fusion. Patients in the trial underwent the following non-surgical care; physical therapy (42%), epidural steroid injections (45%), non-steroidal anti-inflammatory drugs (51%), and opioids (34%).

The rate of crossover in the randomised cohort was 49% at two years. In the observational cohort 97% of patients choosing surgery underwent surgical treatment in the first year. Of those initially choosing non-surgical treatment, 17% underwent surgery by one year and 25% by two years.

Pain

The intention-to-treat analysis of the randomised cohort showed no significant difference between surgical and non-surgical treatment groups at two years for SF-36 bodily pain (MD 1.5 95% CI: –4.2 to 7.3). In contrast the as-treated effects at two years favoured surgery, 17.8 (95% CI, 12.5 to 23.0) in the randomised cohort and 18.5 (95% CI, 13.4 to 23.6) in the observational cohort.

Function

The intention-to-treat analysis in the randomised cohort, showed no significant mean difference between fusion and non-surgical treatment at two years, 1.9 for SF-36 physical function (95% CI -3.7 to 7.5), and 2.2 for ODI (95% CI -2.3 to 6.8) while the as-treated effect significantly favoured surgery. In the randomised cohort for the as treated SF-36 physical function, the effect was 16.7 (95% CI, 11.4

to 22.1) and 19.9 (95% CI, 14.8 to 24.9) in the observational cohort; for the as treated Oswestry Disability Index, the effect was -15.9 (95% CI, -20.2 to -11.7) in the randomised cohort and -17.7 (95% CI, -21.6 to -13.7) in the observational cohort.

Other outcomes

The study by Weinstein (2007)[4] did not report on quality of life, return to work or medication use.

Complications

There was little evidence of harm from either treatment. The most common surgical complication was dural tear (10%). The two-year re-operation rate was 12%.

Discussion

Although this study had a moderate risk of bias, a major limitation was the high degree of crossover from the non-surgical treatment group to surgery. Despite the study performing an intention-to-treat analysis the high rate of crossover would have severely diluted the effect of non-surgical treatment. Furthermore, although the as-treated effect was significant in favour of surgery, there was a high risk of selection bias as the effect of randomisation was negated.

Conclusion

Given the limitations of this study and the paucity of evidence, there is insufficient evidence to confirm whether spinal fusion is as effective as non-surgical treatment in people with CLBP with degenerative spondylolisthesis.

In what conditions or patient groups is spinal fusion indicated?

Three SRs[9, 12, 18] were identified that examined whether certain factors (e.g. psychological subpopulations, smoking status, etc.) were treatment effect modifiers in trials comparing fusion with non-surgical treatment in patients with CLBP.

Comorbid disease

A SR by Choma (2011)[9] examined whether comorbid disease or general health factors such as obesity, smoking, and alcohol and/or drug use were treatment effect modifiers of fusion versus non-surgical treatment in CLBP patients. This review included two RCTs that compared spinal fusion with non-surgical treatment in patients with CLBP,[7, 22] see Table 2 for further detail on the Hagg (2003)[22] and Fairbank (2005)[7] studies. In this review, analyses were performed on a study level; data between studies were not pooled as the studies looked at different subgroups and outcomes were too heterogeneous. Forest plots for standardised mean differences and risk differences with their 95% confidence intervals were constructed comparing fusion to conservative management by subgroup to evaluate whether a treatment worked better in some subgroups than others.

The authors found that non-smokers and patients with no additional comorbidities may respond better to surgical fusion than non-surgical treatment, and recommended optimising the management of medical comorbidities and smoking cessation before considering surgical fusion in CLBP patients. This review had a low to moderate risk of bias due to the lack of information about the search strategy used to identify included studies. In addition to this, the authors of the study noted that their recommendations were based on 'weak' evidence, due to a significant lack of research in this area. The lack of evidence did not allow the authors to draw conclusions on the effectiveness of spinal fusion in comparison to conservative management, but did allow for hypotheses to be generated and considered for clinical decision making and future research planning.

Psychological indications

A SR by Daubs (2011)[12] examined whether fusion was superior to conservative management in certain psychological subpopulations (depression, stress/anxiety, personality disorders) and to determine the most common psychological screening tests and their ability to predict outcomes after treatment in patients with CLBP. This review included one RCT[22] (see Table 2 for further information). In this review, all analyses were performed on a study level; data were not pooled as only one article was identified. For binary outcomes, risk differences and 95% confidence intervals were calculated and a forest plot was constructed comparing fusion to conservative management by subgroup to evaluate whether treatment worked better in some subgroups than others. For studies that reported continuous scores of a particular subgroup at baseline, paired t tests were used to compare the differences in baseline scores between fusion and conservative groups by outcome.

The authors found that patients with depression, neuroticism, and certain personality disorders appeared to respond more favourably to non-surgical treatment and those without a personality disorder more favourably to fusion. This SR had a low to moderate risk of bias due to the lack of information about the search strategy used to identify included studies. In addition, the recommendations of the review are noted to be based on insufficient evidence, meaning that evidence is either unavailable or does not permit a conclusion. The authors of the review note that one study is not enough to make treatment recommendations, but is sufficient to generate hypotheses to be considered in clinical decision making and future research.

Isthmic spondylolisthesis

A systematic review by Wood (2011)[18] examined whether the presence of isthmic spondylolisthesis (IS) modified the effect of treatment (fusion vs. supervised rehabilitation) in patients with CLBP. This review failed to find any studies that compared outcomes between CLBP patients with and without IS, and instead included three RCTs of patients without IS,[3, 7, 20] and two publications relating to one RCT of CLBP patients with IS.[19, 24]

In this review, the focus of the analysis was to evaluate subgroups within larger comparative trials. All analyses were performed on a study level. Data were not pooled because of potentially important differences in patient populations among studies. The standardized mean differences, risk differences and 95% confidence intervals comparing fusion versus multidimensional supervised

rehabilitation were calculated as effect estimates where appropriate. Effect estimates were qualitatively compared visually with forest plots to evaluate whether a treatment worked better in one subgroup compared with the other.

This review found that the presence of IS in patients with CLBP may positively modify the treatment effect of fusion vs. multidimensional supervised rehabilitation with respect to pain and function, however, they classed the overall strength of evidence behind these findings as 'low', meaning that the authors have low confidence that the evidence reflects the true effect, and that further research is likely to change these findings. This review had a low to moderate risk of bias. Variations in the patient populations, interventions, comparators, outcomes length of follow-up for the included studies make generalisation of the findings difficult.

Conclusion

Overall, the three SRs identified do not provide sufficient evidence to conclude that the presence of specific comorbid diseases, general health factors, psychological subpopulations, or isthmic spondylolisthesis are either indications for spinal fusion surgery, or predictors of outcomes in patients undergoing spinal fusion or non-surgical treatment. Neither do they provide sufficient evidence to conclude that spinal fusion is not effective or not indicated in patients with specific comorbid diseases, general health factors, psychological indications, or isthmic spondylolisthesis in addition to CLBP.

Table 2. Characteristics of RCTs of indications/effect modifiers.

Study	Patient population	Intervention	Comparator	Outcomes & other variables
Fairbank 2005[7]	N=349 Age 18-55 years No more than 12 month history of chronic low back pain, with or without referred pain and irrespective of previous decompression or discectomy surgery.	Spinal stabilisation surgery- Particular technique of fusion was left up to the surgeon.	Intensive rehabilitation: daily outpatient program of education and exercise 5 days per week. For 3 weeks continuously. Exercises individually tailored aimed to build upon patients baseline ability. Exercises included stretching of major muscle groups, spinal flexibility exercises, cardiovascular exercises. Principles of cognitive behaviour therapy were used to identify and overcome fears and unhelpful beliefs.	*Outcome measures:* -Back specific pain questionnaire (ODI) -Standardized walking test Secondary outcome measures - SF-36 *Psychological assessment* - DRAM Complications of surgery Work Status *Other variables*: Sociodemographic data: age, gender, duration of back pain, smoking status, litigation, work status, effect of back pain on work Clinical classification: spondylolisthesis, post-laminectomy, CLBP
Hagg 2003[22]	N=264 *3 surgical groups: (n=201)* *1 Non-surgical group* (n= 63) Age 25–65 years Severe CLBP of at least 2 years duration, with no signs of root compression. Patients must have been on sick leave (or have had equivalent disability) for at least 1 year, and non-surgical treatment efforts should	Surgery (fusion): patients allocated to surgery were operated according to one of three commonly used surgical techniques at one or both of the two lower lumbar levels. Group1: non-instrumented posterolateral fusion Group 2: instrumented posterolateral fusion Group 3: instrumented posterolateral fusion +	Group 4: control group, "treated with commonly used non-surgical treatments outlined in a study protocol and executed according to local preferences."	*Outcome measures:* - Patient global assessment of treatment effect - Change of disability (>=50% reduction in ODI score) - Work status *Other variables:* Sociodemographic data: age, sex, occupation, work status, marital status, co-morbidity, workers' compensation, duration of CLBP, duration of sick leave, previous surgery

	have been unsuccessful. A score of at least 7/10 points on the Function and Working disability Score.	interbody fusion		and smoking. Psychological assessment: personality traits (KSP), personality disorders (SCID II), depressive symptoms (ZDS), pain behaviour (Waddell inappropriate signs and symptoms test & UAB Pain Behaviour Scale) Pain assessment: VAS Disability assessment: ODI &GFS Clinical findings: Pain, motor, reflex and sensation Radiography: to identify traction spurs, loss of disc height, vertebral slip, scoliosis and lordosis
Moller 2000[24]/ Ekman 2005[19]	N = 111 Aged 18-55yr Lumbar isthmic spondylolisthesis of any grade, no previous spine surgery, CLBP or sciatica of at least 1 year duration, severely restricted functional ability	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) - Non instrumented patients wore a daytime brace for 6 mo after surgery - No postoperative exercise or physiotherapy program was given	Non operative (n = 34) - 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	*Outcome measures:* DRI Pain index Patient and observer perceived improvement Patient also answered the question: “Would you go through the treatment again now that you know the result?” Global assessment

Are there any reliable diagnostic procedures that predict the success of a fusion operation?

No evidence was identified to answer this question.

DISCLAIMER

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CONFLICT OF INTEREST

The TAC/WSV Evidence Service is provided by the National Trauma Research Institute. The NTRI does not accept funding from pharmaceutical or biotechnology companies or other commercial entities with potential vested interest in the outcomes of systematic reviews.

The TAC/WSV Health Services Group has engaged the NTRI for their objectivity and independence and recognise that any materials developed must be free of influence from parties with vested interests. The Evidence Service has full editorial control.

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