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SYSTEMATIC REVIEW and META-ANALYSIS

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Surgical Versus Nonsurgical Treatment for High-Grade Spondylolisthesis in Children and Adolescents

A Systematic Review and Meta-Analysis

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Abstract: The optimal management of high-grade spondylolisthesis in children and adolescent is controversial. There is a paucity of literature regarding operatively or nonoperative management in this setting.

To assessment of the current state of evidence regarding high-grade spondylolisthesis treatment with the goal of obtaining outcome comparisons in these patients managed either operatively or nonoperatively.

We performed a systematic literature search up to November 2014, using Medline, Embase, and The Cochrane Library. The analysis and eligibility criteria were documented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-guidelines) and Cochrane Back Review Group editorial board. We used the Newcastle–Ottawa quality assessment scale (NOS-scale) to assess the quality.

Five observational studies were considered eligible for analysis based on the evaluation of 1596 identified papers. The mean overall difference in the Scoliosis Research Society questionnaire 22 between the surgical and nonsurgical groups was not statistically significant (95% CI: −0.17 to 0.21, $P = 0.84$). The pooled mean difference in progression of slip between the surgical and nonsurgical groups was no significant difference (OR: 0.47, 95% CI: 0.12–1.81, $P = 0.27$, $I^2 = 0\%$).

Because of the preponderance of uncontrolled case series, low-quality evidence indicates that the quality of life and progression of slips was no significant difference between surgery and nonoperation group. Nonoperative patients had no radiologic progression of their slip during the follow-up period.

(*Medicine* 95(11):e3070)

Abbreviations: CI = confidence interval, HRQOL = health-related quality of life, NOS-scale = Newcastle–Ottawa quality assessment scale, ODI = Oswestry Disability Index, OR = odds ratios, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, SF-12 = Short Form SF-12, SRS-22 = Scoliosis Research Society 22, SRS-30 = Scoliosis Research Society 30.

Editor: Johannes Mayr.
Received: October 11, 2015; revised: February 12, 2016; accepted: February 22, 2016.
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The manuscript has been read and approved by all the authors, who believe that the manuscript represents honest work.
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003070

INTRODUCTION

High-grade spondylolisthesis is a severe spinal deformity in children and adolescents, characterized by a slip of >50% (Meyerding grades III and IV) of the L5-S1 level. The optimal treatment of the pediatric and adolescents with high-grade spondylolisthesis remains challenging and is associated with significant controversies. Several authors support surgical intervention in these patients regardless of symptoms, to prevent slip and symptoms progression.[1–3] However, other authors suggest that nonoperative management can be considered in asymptomatic or less symptomatic high-grade spondylolisthesis.[4–6]

The objective of this study was to evaluate operative and nonsurgical interventions for high grade spondylolisthesis using the changes of health-related quality of life (HRQOL) as a primary outcome measure in a systematic review. A secondary objective was to determine whether there is a difference in clinical outcomes based on the slippage progression.

METHODS

Electronic Literature Database

Prior to the conduction of this systematic review, a detailed protocol was developed. The analysis and eligibility criteria were stated and documented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7] A systematic search was conducted in MEDLINE, EMBASE, and the Cochrane Collaboration Library for literature published from January 1965 through November 2014. Keywords and medical subject headings related to the condition and potential treatment were identified prior to initiating the search. The MESH search terms for MEDLINE included: (nonoperative OR nonoperative management OR operative versus nonoperative OR conservative treatment OR observation OR observational treatment OR brace) AND (operation OR surgical treatment OR surgery OR fusion OR reduction OR fixation OR in situ fusion OR operative procedures) AND (Spondylolisthesis OR Spondylolisthesis OR high-grade spondylolisthesis OR isthmic spondylolisthesis OR severe spondylolisthesis OR spondylolysis OR lumbar spondylolysis OR grade iii, grades iv, v). Gray literature, including books and conference papers, was collected and these studies were included if they met inclusion criteria. No linguistic restriction was imposed on the search as recommended by the Cochrane Back Review Group editorial board.[8] The unpublished investigations were not included.

Inclusion Criteria and Study Selection

We systematically reviewed published studies according to the following criteria: high-grade lumbosacral spondylolisthesis or spondyloptosis as defined by a Meyerding classification of III or greater; subjects who were 18 years or younger at initial presentation; a minimum of 18-month follow-up was required for surgical and nonsurgical patients; the study reported at least 1 desirable outcome, including health-related quality of life, or progression of slip; the types of treatment included surgical (spinal fusion with or without instrumentation) and nonsurgical interventions, study design: randomized controlled trials (RCTs) and observational studies (cohort studies, case-control studies, and cross-sectional studies). Excluded criteria were as follows: editorials, comments, case reports, and conference were excluded. Patients with dysplastic spinal deformities, such as neurofibromatosis, severe developmental delay who would be unable to complete the outcome questionnaire were excluded.

Two authors performed independent review of the abstracts for inclusion or exclusion (XXH, LL). References were recommended for full text review if the study was expected to provide evidence to answer the clinical questions. The summarized results were cross-checked again. Disagreements were solved by consensus with the third author (WXC).

Quality Assessment

The Newcastle–Ottawa quality assessment scale (NOS-scale) was used to assess the quality of the included studies.[9] The NOS scale assigns a maximum of 8 points for case-control studies and 9 points for cohort studies. Points are not only given for selection of participants and measurement of exposure, but also for comparability of cohorts and assessment of outcomes and follow-up. Validity scores of NOS-scale were evaluated as follows: 8 to 9, high quality; 6 to 7, medium quality; 5, low quality.

Data Collection

Data extraction was undertaken by 2 independent reviewers (XXH and LL). Some articles were excluded on the basis of information provided by the title or abstract if they clearly fit one of the exclusion criteria. The basic information of participants in each original study was collected in a specifically developed data form, which included demographics, study design, diagnosis, baseline and change in assessment scale, and the progression of slip. Disagreements were resolved by consensus with a third author (WXC). The details are shown in Table 1.

Data Analysis

A meta-analysis was performed on the extracted data with RevMan 5.0 software (Cochrane IMS). A random-effect model was employed for studies that showed homogeneity. For dichotomous variables, the odds ratio (OR) and 95% confidence interval (CI) were calculated. The presence of heterogeneity was assessed by χ^2 test, which was affirmed if P value was less than 0.05. The I^2 statistics were used to test heterogeneity. An I^2 value <25% was considered to be homogeneous, 25% to 50% as low heterogeneity, 50% to 75% to be of moderate heterogeneity, and more than 75% as high heterogeneity.

RESULTS

Search Results

The flow chart shows the study selection process (Figure 1). Initially, 1596 articles were included by search

TABLE 1. Characteristics of Included Studies

Study	Setting			Participants					Intervention		
				No. of Patients		Mean Age (Yr)		Mean follow-up (yrs)			
	Design	Location	Enrollment	Surgery	Non-OP	Surgery	Non-OP	Surgery	Non-OP	Surgery	Non-OP	Outcomes
Bourassa-Moreau 2013[10]	Observational case series	Canada	2002–2011	23	5	15.0 ± 2.7	16.0 ± 1.8	3.0 ± 1.4	4.5 ± 1.4	PLIF with decompression; bone graft	observation	HRQOL; Neurologic examination, radiographic evaluation
Bourassa-Moreau 2010[13]	A prospective database	Canada	2002–2009	29	5	15.1 (7.8–20)	16 (13.3–18)	1.56	2.5 (0.83–4.75)	primary fusion with or without instrumentation	observation	HRQOL
Lundine 2014[11]	Retrospective cohort study	Denmark	2001–2010	34	15	12.4 ± 2.2	12.9 ± 1.8	7.5 ± 4.0	7.6 ± 3.5	Fusion In situ: PLF;ALIF; Reduction	Brace (14 pts)	Radiological measured; HRQOL; compli –cation rate
Harris 1987[6]	Retrospective cohort study	American	1938–1980	21	11	17.1 (11–25)	17.8 (10–24)	18 (3–42)	23.6 (4–45)	posterior interlaminar fusion; bone grafts	brace (Half of the pts in short period)	Radiological measured Progression of slip
Seitsalo 1991[12]	Retrospective cohort study	Finland	1948–1980	83	4	14.3 (1–19)	14.3 (1–19)	14.5 (5–32)	14.8 (5–32)	Fusion in situ: laminectomy; PLF; ALIF; No reduction	Rest or restriction of activities; observation	Radiological measured; Progression of slip

ALIF = anterior lumbar interbody fusion; HRQOL = health-related quality of life; non-OP = nonoperation; PLF = posterolateral fusion; PLIF = posterior lumbar interbody fusion.

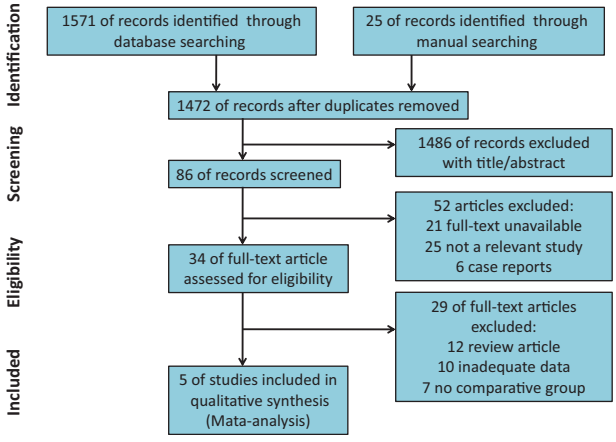

FIGURE 1. Flow chart of identifying and including studies.

strategy. After reviewing titles and abstracts, 86 articles remained for screening based on the inclusion criteria. Of these 86 articles, 34 full text articles were selected for further evaluation. Twenty-nine studies were excluded after reviewing full-texts. Finally, 5 eligible studies were identified, consisting of 1 observational case series,[10] 1 prospective database,[13] and 3 retrospective cohort studies.[6,11,12] Table 1 provides a summary of characteristics of these studies, including author, year of publication, nation, and study design, number of patients, follow-up time, operative or nonoperative intervention, and clinical outcome. Of the 5 articles selected for inclusion, 3 studies measured the outcome of the treatment on the HRQOL (questionnaire) and 2 studies measured radiographic evidence of progression of slip. In 1 retrospective study, 272 children and adolescents with spondylolisthesis were enrolled, including 87 patients with high grade slips.[12] The progression of slip was described between operation and nonoperation groups.

Risk of Bias of Included Studies

The average follow-up of the trials ranged from 1.56 to 23.6 years. The studies showed in general problems with follow-up and missing data for each variable of interest. The quality of the studies was in general considered low[10] or moderate[6,11,13] ranging from 5 to 7 points according to the NOS-scale (see Table 2). One study was judged as a high-quality study with 8 points.[12]

About the indication for operative treatment, 2 studies were based on the physician's own criteria for recommending surgical management.[10,13] In another study, patients with persistent low back pain or radiating pain or progression of the slip to 30% of the body of the slip vertebra were included to consider surgical treatment.[12] Lundine et al[11] suggested that the patients with significant dysfunction and deformity, progressive pain, and neurologic compromise should be strongly considered for operative intervention. In their opinion, conservative management did not lead to a large group of dissatisfied for growing patients with high-grade slips.

Quantitative Results of the Meta-Analysis

There is increasing emphasis on the use of HRQOL outcome measures to determine the efficacy of treatment, particularly for diseases that are not life threatening but affect the patient's quality of life. The cumulative meta-analytic comparison was carried about the outcome of the treatment. The assessment scale of HRQOL, including Scoliosis Research Society 22 (SRS-22), Short Form SF-12 (SF-12), and Scoliosis Research Society 30 (SRS-30) as an outcome evaluation was reported in 3 inclusive studies with a total of 111 patients. The result showed no heterogeneity ($I^2 = 0\%$) and the random effect pooled OR was 0.02(95% CI: −0.17 to 0.21, $P = 0.84$). No significant difference was found between the surgical and nonsurgical groups in the SRS-22 domains (Function) (Figure 2A). There is no significant difference between the surgical and nonsurgical groups in other 2 SRS-22 subscores, including Pain and Satisfaction domains (Figure 2B and C). The random-effect pooled OR was −0.14 (95% CI: −0.32 to 0.14, $P = 0.13$) with low level of heterogeneity ($I^2 = 21\%$) in the SRS-22 domains (mental health) between the surgical and nonsurgical groups (Figure 2D).

The pooled mean difference in progression of slip (Figure 3) between the surgical and nonsurgical groups was in favor of surgery (OR: 0.47, 95% CI: 0.12–1.81, $P = 0.27$, $I^2 = 0\%$). However, no significant difference was shown between the surgical and nonsurgical groups.

Clinical Outcomes

A prospective controlled trial reported by Bourassa-Moreau applied Short Form (SF)-12 assessment scales to evaluation the quality of life for patients with high grade slipage.[10] They suggested the SF-12 physical and mental composite scores were significantly higher in the nonoperative group initially. However, SF-12 scores in both groups became similar at last follow-up.

In a retrospective study, Harris and Weinstein[6] reported the long-term outcome of patients with Grade-Ill and IV spondylolisthesis. In nonsurgery group, when the patients were asked to compare the symptoms at follow-up with the initial presenting symptoms, 27% were unchanged, 36% were improved, and 36% had become worse with time. None of the patients were dissatisfied with their physical appearance. Eighteen percent of

TABLE 2. Quality Assessment of Selected Studies According to NOS-Scale

Study	Election 4 Point	Comparability 2 Point	Outcome/Exposure 3 Point	Total 9 Point
Lundine[11]	2	1	3	6
Harris[6]	3	1	2	6
Bourassa-Moreau[10]	2	1	2	5
Seitsalo[12]	3	2	3	8
Bourassa-Moreau[12]	3	1	3	7

NOS-scale = Newcastle–Ottawa quality assessment scale.

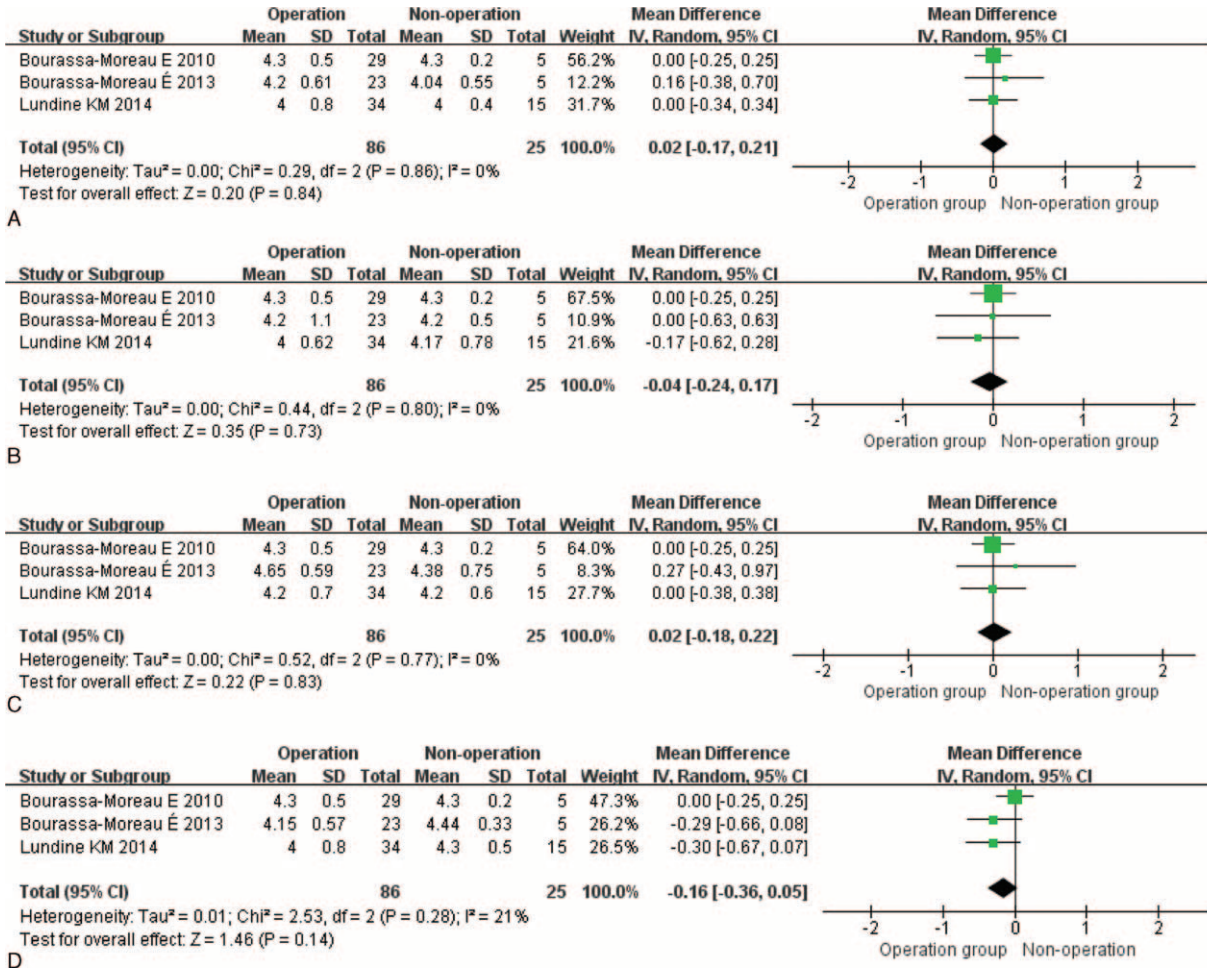

FIGURE 2. SRS-22 domains. A, Function improvement between operation and nonoperation groups, no significant difference was observed for overall effect. B, Pain change, between operation and nonoperation groups, no significant difference was observed for overall effect. C, Satisfaction with management of operation versus nonoperation for the treatment of high-grade spondylolisthesis, no significant difference was found. D, Mental health between operation and nonoperation groups, favoring operation with higher mental health scores, but no significant difference was found. SRS-22 = Scoliosis Research Society questionnaire 22.

patients stated that the spondylolisthesis had not influenced their choice of occupation, while 36% of patients had influenced the choice of occupation. In surgery group, 19% were unchanged, 76% were improved, and only 1 patient markedly symptomatic at the time of follow-up. Thirty-three percent of patients stated that the spondylolisthesis had not influenced their choice of occupation, while half of all had influenced the choice of occupation.

DISCUSSION

Several previous reviews described the comparison between surgery and conservative management for patients with low-grade spondylolisthesis or degenerative spondylolisthesis.[14–16] There is no consensus regarding the best management of high-grade slippage in patients. Few published studies have compared the outcomes of surgery or nonoperation in patients with severe spondylolisthesis. This study sought to

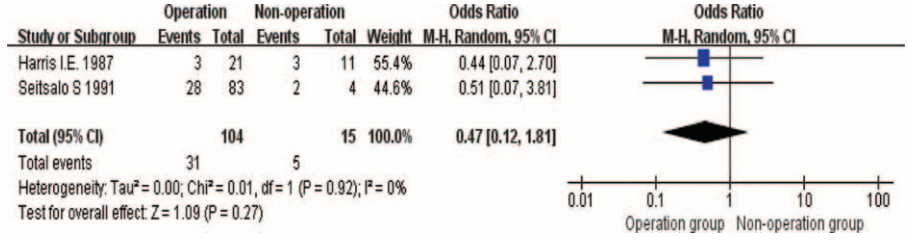

FIGURE 3. Forest plot: mean difference in progression of slip and 95% CI for surgical versus nonsurgical treatment. CI = confidence interval.

review the clinical outcomes in patients with high-grade slips managed either operatively or nonoperatively.

Nonoperative management of high-grade spondylolisthesis includes bracing and physiotherapy. Good results have been reported with the use of a brace,[17,18] exercise programs,[16,19] and mixed conservative treatments.[20–22] However, these studies commonly have been retrospective with different populations of patients. It limits the validity of the conclusions. It has been shown that patient's outcome is highly influenced by the method used to measure it. For some patients with high-grade spondylolisthesis, the most important symptom is pain, which is subjective and difficult to quantify. Moreover, there is a tendency for spontaneous improvement with time.[23] Harris and Weinstein[6] reported the long-term outcome of 11 patients who had high-grade spondylolisthesis and were never operated on. They highlighted that these patients only required minor adjustment to remain functional in their occupations. No evidence was provided for the need of prophylactic fusion of asymptomatic high-grade spondylolisthesis. It is a pity that they did not have standardized questionnaires to assess the quality of life.

The indications for surgery were persistent low back pain, radicular pain, severe displacement, a majority of impairment of quality of life or slip progression.[4,24] The results from surgical management of high-grade spondylolisthesis usually have been reported as satisfactory and preferable.[25–27] However, based on a recent Scoliosis Research Society morbidity and mortality database review, surgical intervention in patients with spondylolisthesis comes with more than 10% complication risk.[28] In addition, surgical intervention to reduce the slip percentage has been associated with an increased risk of neurological deficit,[28] although correction of the kyphotic slip angle is probably more important than reduction of slip.[29,30] The literature supports that some patients with good quality of life were selected to undergo surgery; the results showed no improvement of quality of life on SRS-22 and SF-12 postoperatively.[11] It shows that surgery has the greatest impact for patients with significant impairment in their quality of life, while it may provide only minor improvement for those with a relatively normal quality of life at initial presentation.

In our analysis, 3 studies showed that quality-of-life questionnaires were similar between the 2 groups at last follow-up. The evaluation domain included function, pain, satisfaction, and mental health. There was no worsening of quality of life in nonoperative patients during follow-up. Operative intervention for the symptomatic patient achieves similar long-term results compared with patients whose minimal symptoms do not warrant surgery. Delayed surgical intervention does not result in worse outcomes. The progression of slips was no significant difference between surgery and nonoperation group in the 2 studies by Harris and Seitsalo.[6,12] Other 2 studies showed that none of the nonoperative patients had radiologic progression of their slip during the follow-up period.[11,13] Therefore, nonoperative management or close observation of the patients with a high-grade spondylolisthesis does not lead to significant problems.

For the assessment of HRQOL, the Oswestry Disability Index (ODI) scores were usually applied to patients with spondylolisthesis, while the SRS-22 and SRS-30 score scales were usually applied to patients with scoliosis. However, the 5 subscores of them including pain, function, mental health, self-image, and satisfaction with management were also applicable to patients with high-grade spondylolisthesis. On one hand, the SRS questionnaire scores have been found to correlate significantly with ODI scores in this population of patients.[31] On the other hand, the ODI score scale only focuses on pain and function, not involving patient self-image, mental health, or satisfaction. However, the SRS-22 questionnaire scores include all of these factors. In addition, the mental health component questions have been adapted from the well-validated SF-12 questionnaire. The SRS-30 questionnaire contains all questions within the SRS-22.

The implications of the study are quite significant. First, the well-designed and strong evidence studies to evaluate operative and nonsurgical interventions for high-grade spondylolisthesis were very rare. Publications available for this study were very limited. Second, the bias inherent to retrospective and other nonrandomized studies existed. The operative group could have a greater percentage of patients with a larger slip grading or more severe chief complaint. Furthermore, the complications of surgical or nonsurgical treatment were absent in assessment of clinical outcomes. The last and most important point, the publication bias, was present. It might explain why there are only few studies mentioning the absence of significant differences in slip progression between conservative and surgical treatment groups.

CONCLUSIONS

Because of the preponderance of uncontrolled case series, low-quality evidence indicates that the quality of life and progression of slips was no significant difference between surgery and nonoperation group. Nonoperative patients had no radiologic progression of their slip during the follow-up period.

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