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REVIEW ARTICLE

Surgery for adult spondylolisthesis: a systematic review of the evidence

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Abstract Surgery for isthmic and degenerative spondylolisthesis (SL) in adults is carried out very frequently in everyday practice. However, it is still unclear whether the results of surgery are better than those of conservative treatment and whether decompression alone or instrumented fusion with decompression should be recommended. In addition, the role of reduction is unclear. Four clinically relevant key questions were addressed in this study: (1) Is surgery more successful than conservative treatment in relation to pain and function in adult patients with isthmic SL? (2) Is surgery more successful than conservative treatment in relation to pain and function in adult patients with degenerative SL? (3) Is instrumented fusion with decompression more successful in relation to pain and function than decompression alone in adult patients with degenerative SL and spinal canal stenosis? (4) Is instrumented fusion with reduction more successful in relation to pain and function than instrumented fusion without reduction in adult patients with isthmic or degenerative SL? A systematic PubMed search was carried out to identify randomized and nonrandomized controlled trials on these topics. Papers were analyzed systematically in a search for the best evidence. A total of 18 studies was identified and analyzed: two for question 1, eight for question 2, four for question 3, and four for question 4. Surgery appears to be better than conservative treatment in adults with isthmic SL (poor evidence) and also in adults with degenerative SL (good evidence). Instrumented fusion with decompression appears to be more successful than decompression alone in adults with degenerative SL and spinal stenosis (poor evidence). Reduction and instrumented fusion does not appear to be more successful than instrumented fusion without reduction in adults with isthmic or degenerative SL (moderate evidence).

Keywords Spondylolisthesis · Degenerative spondylolisthesis · Isthmic spondylolisthesis · Surgery · Conservative treatment · Adults · Fusion · Decompression · Reduction

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Introduction

Treatment for lumbar spondylolisthesis (SL) in adult patients is a frequent challenge in everyday work for spinal physicians. In adult patients, the most frequent types of SL are degenerative type 3 and isthmic type 2 in the Wiltse and Rothman classification [1], corresponding to the acquired degenerative type and the dysplastic developmental type or chronically acquired traumatic type in the Marchetti and Bartolozzi classification [2]. Data on the natural history of

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degenerative SL, spondylolysis, and isthmic SL are very scarce [3–5]. Although both pathologies have a high level of prevalence and treatments are therefore very frequent, certain problems are still unresolved.

Degenerative lumbar SL (Fig. 1a) means slippage of a cranial vertebra over a caudal one, due to disc degeneration and zygapophyseal joint arthropathy, often in combination with spinal canal stenosis. It is most frequently located at L4/L5 in women over 60 years of age [6, 7]. Patients usually report a combination of low back pain (LBP) and radiating pain (pseudoradicular pain, radicular pain, spinal claudication), and accompanying neurological deficits are possible.

Isthmic SL (Fig. 1b) is usually located at L5/S1. Commonly, there is an osseous defect at the isthmus of the vertebral arch (pars interarticularis) of the L5 vertebra, leading to more or less serious instability of the inferior articular process and segmental instability, with degeneration of the zygapophyseal joints and the disc. The full underlying pathogenesis is still unclear, and several risk factors are involved—such as genetic factors, intense exercise with hyperextension, etc. [8]. Patients present to physicians as young adults with LBP and/or radiating leg pain, possibly with neurological deficits.

Whereas degenerative SL occurs more often in females, isthmic SL is more frequent in males, with radiographic prevalences of about 4–12 % for isthmic SL and up to about 40 % for degenerative SL in Caucasian populations [8, 9]. Radiographic observations are not necessarily associated with any clinical symptoms in either of the conditions [9].

In symptomatic patients, which patients should undergo surgery and which should receive conservative treatment is still an open question—as is the question of which surgical technique is best [7, 10–12]. Conservative treatments may include various types of nonsurgical therapy, such as medication, physiotherapy, weight loss, external orthosis, injections, etc. [7]. Surgical treatment appears to be indicated when conservative treatments fail and when serious neurological deficits are present and there is substantial and progressive slippage. Various types of surgery, including decompression and stabilization techniques, have been proposed. Several reviews have focused on treatment strategies [13], but the basis for these in controlled trials is small.

The purpose of this study was to investigate the evidence for surgery of adult SL based on the available literature, with a focus on four key aspects that are of major relevance in everyday decision-making for spinal surgeons.

Materials and methods

On the basis of the practical situation of consulting and discussing treatment options with the patient, four structured and relevant key questions were formulated using the "patient, intervention, comparison, outcome" (PICO)

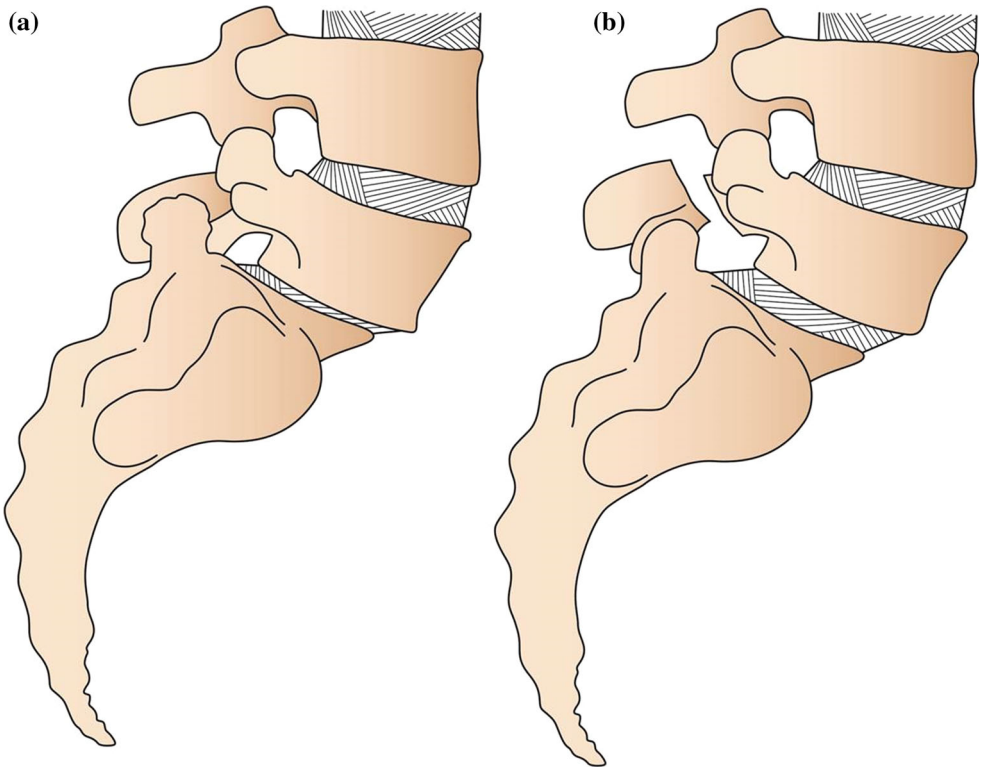

Fig. 1 **a** Degenerative spondylolisthesis L5/S1; **b** Isthmic spondylolisthesis

scheme developed at McMaster University (Hamilton, Ontario) [14, 15]:

- Is surgery more successful than conservative treatment in relation to pain and function in adult patients with isthmic SL?
- Is surgery more successful than conservative treatment in relation to pain and function in adult patients with degenerative SL?
- Is instrumented fusion with decompression more successful in relation to pain and function than decompression alone in adult patients with degenerative SL and spinal canal stenosis?
- Is instrumented fusion with reduction more successful in relation to pain and function than instrumented fusion without reduction in adult patients with isthmic or degenerative SL?

A systematic PubMed search of the available literature was carried out on 03 November 2013 (including literature from 1966 up to that date) to identify randomized and nonrandomized controlled trials. The search terms included descriptions of the pathology, of the anatomic location, of the type of study, and of the type of treatment. The following search string was entered:

- (spondylolysis[MeSH Terms] OR spondylolys*[Text Word] OR spondylolisthes*[Text Word]) AND (lumbar[Text Word] OR lumbosacral[Text Word]) AND (spinal fusion[Mesh Terms] OR spinal fusion[Text Word] OR surgery[MeSH Subheading] OR surgical procedures, operative[MeSH Terms] OR general surgery[MeSH Terms] OR surgery[Text Word] OR conservative[Text Word] OR exercise*[MeSH Terms] OR exercise*[Text Word] OR physical therapy modalities[Mesh Terms] OR physiotherapy[Text Word] OR pain management[MeSH Terms] OR pain therapy[MeSH Terms] OR medication[Text Word]) AND (randomized controlled trial[Publication Type] OR controlled clinical trial [Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR

Fig. 2 Results of literature search

drug therapy[MeSH Subheading] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]).

Inclusion criteria for the final analysis were: controlled trial; inclusion of groups that were compared exactly meeting the four key questions; English language; minimum follow-up period 1 year. Exclusion criteria were: studies on pediatric or adolescent patients; reviews; studies with a different focus (e.g., fusion rate, rehabilitation, diagnosis, epidemiology, pathogenesis, body mass index, age, complications, navigation); studies comparing different types of fusion, instrumentation, or decompression; technical notes; case reports; biomechanical or animal studies; and studies including only conservative treatment.

The titles and abstracts and in case of doubt also full papers were screened for relevance. Publications that met the inclusion criteria were analyzed in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) checklists [16], based on recommendations by the Guidelines International Network [17], and the PRISMA checklist [18]. Data were extracted according to a predetermined form (Supplementary material 1, 2). Each study was evaluated by one orthopedic spine surgeon and one neurosurgical spine surgeon. In cases of disagreement, a clarifying moderated discussion was held to reach agreement. Levels of evidence were assigned in accordance with the Oxford Centre for Evidence-Based Medicine (OCEBM) criteria [19].

Results

A total of 426 trials were identified by the systematic search using the defined criteria. All of these trials were analyzed to determine whether they met the additional inclusion criteria, and 408 publications were excluded for the reasons specified in Fig. 2. A total of 18 publications ultimately met the inclusion criteria and were entered into the final analysis. Two of these publications were relevant for key question no. 1 [20, 21], eight for question 2 [22–29], four for question 3 [30–33] and four for question 4 [34–37] (Fig. 2). The results of the literature analysis for answering key questions nos. 1–4 are presented in Supplementary material 1 and 2.

Both of the publications identified in relation to question 1 are concerned with the same study—evidence-based medicine (EBM) level 1b, randomized controlled trial (RCT)—of a relatively modest number of patients ($n = 111$), presenting follow-up results for 2 years in one case and for 9 years in the other, both favoring surgery over conservative treatment [20, 21].

Of the eight publications identified in relation to question 2, one is a level 2b cohort study of 53 patients, presenting better results for surgery than for conservative treatment, but with methodological deficiencies [23]. A second publication describes the results for 75 patients in a level 1b RCT, comparing the insertion of an interspinous process decompression device (X STOP) with conservative treatment [22]. According to this study, patients benefit more from surgery than from conservative treatment. The remaining six publications present results and subanalyses from the Spine Patient Outcome Research Trial (SPORT), a well-conducted and relatively large (with over 1200 patients) level 1b RCT. Their conclusion is that surgery performs better than conservative treatment [24–29].

All four studies relevant to question 3 showed serious methodological deficiencies. In a comparatively old series (1985–1990), Bridwell et al. presented only 43 patients in a level 2b cohort study, which showed that instrumented fusion with decompression appears to be better than decompression alone [30]. Ghogawala et al. published the results for only 34 patients in a level 2b cohort study, with similar findings [32]. Park et al. included a total of only 45 patients in a retrospective level 3b case–control study that had substantially different baseline data, so that their results are poorly applicable for answering the key question [33]. Finally, Försth et al. presented results from a quite large registry study (1306 patients; level 3b case–control study) without differentiating between instrumented and non-instrumented fusion and without differentiating between baseline symptoms in all the groups [31]. Their conclusion, that fusion and decompression did not perform better than decompression alone, thus needs to be interpreted with great caution.

The four publications relevant for question 4 include the well-conducted level 1b RCT by Benli et al., which concludes that reduction does not provide clinical benefits in patients with isthmic SL, although the study sample of only 40 patients is rather small [34]. Lian et al. contribute two methodologically well-conducted level 1b RCT studies, one for isthmic SL ($n = 88$) and another for degenerative SL ($n = 73$), showing that reduction does not provide better clinical outcomes than in situ fusion with either type of pathology [36, 37]. The article by Hagenmaier et al. presents selected data from two ongoing prospective studies [35]. In this level 2c study setting, they did not compare separate groups but performed a correlation analysis for the complete cohort ($n = 72$), without finding any significant correlation between the grade of reduction and the clinical outcome for grade 1 and 2 isthmic or degenerative SL.

Discussion

This study focused specifically on four key questions that are of clinical relevance for everyday practice. Several reviews have investigated degenerative and isthmic SL in an effort to identify evidence that would allow treatment recommendations to be made [12]. However, these reviews do not precisely address the four key questions. The present study was therefore carried out in order to fill the gap.

There seems to be a wide discrepancy between the large numbers of operations for lumbar SL that are carried out throughout the world, on the one hand, and the small amount of evidence with clear data supporting these treatments, on the other. The increasing numbers of spine operations are currently being criticized and there has been public questioning of the indications for spinal surgery. In addition to medical issues, it has even been suggested that there might be economic factors influencing surgeons' decision-making. In view of these debates, key questions nos. 1 and 2 are particularly relevant.

Question 1: Surgery vs. conservative treatment in adult patients with isthmic SL

Only a single study relevant to answering question 1 was found, with the results presented in three papers [20, 21, 38]. The study was methodologically well designed and conducted. However, a large group of patients received uninstrumented posterolateral fusion—a technique that is no longer really performed in large groups of patients in many countries. The study shows better results for surgery in comparison with conservative treatment after a 2-year follow-up period, with the results for surgery after a 9-year follow-up period being still better, although in smaller numbers. The latest analysis from the study, focusing on adjacent segment degeneration (ASD), no longer provided clear comparisons of the original groups (surgery vs. exercise) [38]. According to the analysis, the incidence of ASD was lower in the exercise group; instrumentation vs. non-instrumentation did not affect the prevalence of ASD; and the functional outcome for patients with ASD was slightly poorer than for those without ASD.

Overall, the available evidence for surgery in relation to question 1 is fairly poor, and the recommendation for surgery is therefore weak.

Question 2: Surgery vs. conservative treatment in adult patients with degenerative SL

To answer key question no. 2, eight papers were found that met the inclusion criteria for the review [22–29]. However, the eight papers were based on only three different studies. Six papers evaluated data from the Spine Patient Outcome Research Trial (SPORT) [24–29], focusing on various aspects, but still dealing with the same cohort. As degenerative SL has a much higher prevalence than isthmic SL, trials on degenerative SL are easier to perform and more frequent than trials on isthmic SL. Nevertheless, the small amount of high-quality data is surprising and notable.

The SPORT trial is a well-conducted multicenter study with randomized and additional observational groups. The study design and analysis are good. Due to high rates of cross-over, only the pooled as-treated analysis from the randomized and observational arms is relevant for answering key question 2. The level of evidence (LoE) is therefore 2b, rather than the 1b aimed for. Six papers describe certain aspects of the SPORT trial in a well-conducted way, but all of the papers are based on the same cohort. In 2007, Weinstein et al. reported that surgery was better than conservative treatment after 2 years of follow-up [28]; in 2009, the same group reported the same finding at the 4-year follow-up [29].

In 2008, Pearson et al. focused on radiographic subgroups (listhesis grade, disc height, segmental mobility), but did not identify any relevant effects of radiographic features [26]. This paper does not provide any additional data for answering question 2.

In 2010, Pearson et al. compared patients with degenerative SL with those with spinal stenosis without SL and found that surgery performed better than conservative treatment after 2 years in both groups, with a better treatment effect for patients with degenerative SL [25]. Strictly speaking, this paper does not add additional data for answering question 2, as it is based on the same patients as the original study by Weinstein et al. [28].

In 2011, Pearson et al. carried out another subanalysis of the SPORT trial, focusing on differences in baseline symptoms (predominant leg pain, predominant low back pain, equal leg and back pain) [24]. The authors found that there were greater improvements in patients who had predominant leg pain at baseline. However, no additional data are provided that would be of relevance to question 2.

In 2013, finally, Pearson et al. published an additional subanalysis of the SPORT trial, identifying a group of predictive factors for greater beneficial effects of surgery (age under 67 years, female sex, absence of stomach problems, neurogenic claudication, reflex asymmetry, opioid use, not taking antidepressants, dissatisfaction with symptoms, anticipation of a high likelihood of becoming pain-free after surgery) [27]. With regard to key question 2, no additional data can be presented, as the basic cohort is the same as that in Weinstein et al. [28].

The study by Matsudaira et al. was not randomized, with an LoE of 2b; it had several methodological shortcomings,

including a small cohort, considerable baseline differences between the groups being compared, no clear definition of conservative treatment, and use of a surgical technique that is rarely applied (laminoplasty) [23]. According to the study, surgery tended to be better than conservative treatment, with no relevant benefit from instrumentation.

The X STOP study by Anderson et al. has some methodological deficiencies (a small cohort, level of baseline symptoms rather low, no clear description of symptoms, main author a consultant for and stockholder of the company that manufactures the X STOP device). However, it concludes that patients with grade 1 degenerative SL and spinal stenosis benefit from X STOP more than from conservative treatment [22].

In conclusion, therefore, key question 2 can be answered as follows: on the basis of the three studies included (the well-conducted SPORT trial, a poorly performed cohort study, and the X STOP trial with methodological shortcomings), surgery rather than conservative treatment can be recommended for adult patients with degenerative SL, with relatively good evidence. This corresponds well with the recommendation by Watters et al. (North American Spine Society evidence-based clinical guideline) [39].

Question 3: Instrumented fusion with decompression vs. decompression alone in adult patients with degenerative SL and spinal canal stenosis

Only four studies were found that met the inclusion criteria to answer key question no. 3 [30–33].

Försth et al. presented data with large numbers of patients from the Swedish National Spine Register, SweSpine. However, this registry study (3b, case–control study) does not present baseline data for the two groups on which the key question focuses—patients with degenerative SL who underwent decompression alone, or those with decompression and instrumented fusion [31]. In addition, fusion patients are not distinguished relative to instrumentation or non-instrumentation. Strictly speaking, therefore, despite the large cohort, the study is not able to answer question 3; at best, a trend can be speculated on that fusion may not be necessary for all patients with degenerative SL.

Park et al. presented a retrospective 3b case–control study with many methodological shortcomings—e.g., different baseline data, especially in relation to numerical rating scale (NRS) back pain, and very small groups. The study is therefore not useful for answering question 3 [33].

Ghogawala et al. published a prospective 2b cohort study, with small groups and several methodological deficiencies [32]. The decision on which type of surgery to carry out was made at the surgeon's discretion. Overall, the study provides support for fusion on a very weak basis.

In 1993, Bridwell et al. presented a prospective 2b cohort study with small groups, rather old surgical techniques, and no comparable baseline data [30]. Nevertheless, the study supports fusion on a weak basis.

Overall, key question no. 3 can be answered with support for fusion, on a weak basis. This result corresponds well with the available guidelines [40, 41].

Question 4: Instrumented fusion with reduction vs. instrumented fusion without reduction in adult patients with isthmic or degenerative SL

Only four studies were identified that met the inclusion criteria for answering key question no. 4 [34–37].

In 2006, Benli et al. presented a prospective 2b cohort study on dysplastic low-grade or high-grade SL [34]. The study was well conducted, but the groups were small; the authors concluded that reduction did not have any favorable effects on clinical outcomes.

In 2013, Lian et al. presented a well-designed and well-conducted 1b RCT in the *Spine Journal,* focusing on patients with degenerative SL (Meyerding grades I or II) who underwent posterior lumbar interbody fusion, with or without reduction [37]. Repositioning did not provide better clinical results in comparison with instrumented in situ fusion.

In 2014, the same group published a study in the *European Spine Journal,* focusing on patients with adult isthmic SL (Meyerding grades I, II or III) who underwent posterior lumbar interbody fusion, with or without reduction [36]. This trial is also a well-designed and well-conducted 1b RCT. Again, repositioning was not found to provide better clinical results in comparison with instrumented in situ fusion.

Hagenmaier et al. published data from two ongoing prospective trials in patients with degenerative or isthmic spondylolisthesis; they performed a correlation analysis, which did not find any significant positive effects of reduction on the clinical outcome after 1 year of follow-up [35]. Strictly speaking, this study is not a controlled trial and it has several shortcomings. However, its correlation analysis deserves to be included.

In conclusion, therefore, key question no. 4 can be answered by stating that there is moderate evidence to show that repositioning does not provide any clinical benefit. With regard to degenerative SL, this corresponds well to the recommendation given by Watters et al. (North American Spine Society evidence-based clinical guideline) [39]. It should be emphasized that particularly in patients with high-grade spondylolisthesis and an unbalanced spine (Spinal Deformity Study Group type 6), reduction and realignment appears to be mandatory [42] including reduction of local kyphosis. However, there are still no

large clinical controlled trials to confirm this. Future studies that hopefully will make use of the classification of Labelle and Mac-Thiong [42] will need to produce better evidence in this field.

One limitation of the present analysis is that the possibility cannot be ruled out that the search strategy might have missed some publications. The search was limited to PubMed, as it was assumed that any authors who carried out a study of the required quality (a controlled trial) would certainly have published their work in a journal that is included in PubMed. A second limitation is the fact that due to the very limited number of studies that could be included for each key question and due to the very heterogeneous target variables a meta-analysis was not performed. The focus of the presented data is therefore set on the individual studies.

In addition, the risk of bias across studies [18] is very hard to specify. It needs to be emphasized that rather old surgical techniques such as fusion without instrumentation [20, 21] could create such a bias. A strong multicenter study such as the SPORT trial [24–29] with its logistic background may have better chances to publish their results in multiple papers than research groups with reduced logistics. Limited clear descriptions of baseline complaints in patients may be a bias across studies [30, 31] as well as different baseline data of groups [23, 30] and also non-uniform instruments to assess outcomes. Some studies do not differentiate between leg pain and back pain [22, 30, 32, 34, 36, 37]. No study clearly described the pain medication of patients during the study and its influence on their results. The latter point is of major relevance for studies on surgical treatments of pain problems. In addition, it may be speculated that most active research groups in the field of spine surgery tend to promote surgical techniques rather than conservative treatments. The bias and impact of reimbursement for surgery versus conservative treatment may also be of interest, especially when the main author is consultant and stockholder of the company manufacturing the implant that is studied [22]. Lastly, the numbers of patients included into each study vary remarkably from 10 patients per group [34] up to 655 [31] creating a bias.

In 2012, Kleinstueck et al. published a study based on prospectively collected data (2004–2008), with a 1-year follow-up period, for patients with lumbar degenerative SL; decompression and fusion were compared with decompression alone [43]. A total of 213 consecutive patients (mean age 69 years, 73 % female) met the inclusion criteria (i.e., lumbar degenerative SL, maximum of three affected levels, no previous surgery at the affected level); 56 underwent simple decompression (the D group) and 157 received decompression and fusion (the D&F group). Before surgery, the patients in the D&F group had slightly but significantly poorer scores for lower back pain (LBP) and for the Core Outcome Measures Index (COMI) than the patients in group D. There was greater improvement in COMI at the 1-year follow-up examinations in the D&F group than in the D group. The extent of the reduction in leg pain did not differ at the follow-up, but LBP improved significantly more in group D&F. Overall, patients with decompression and instrumented fusion showed better clinical results than those with decompression alone, regardless of the baseline symptoms.

Since only limited data are available from controlled trials, alternative strategies for defining appropriate treatments for certain types of patients have been used—e.g., using the RAND appropriateness method [11, 44].

A few papers have compared the effect of fusion and decompression with fusion without decompression [45]. However, these data are not included here, since fusion without decompression no longer appears to be a common technique in most centers for patients with degenerative SL, and from a realistic point of view, surgeons would not risk omitting decompression in patients with proven symptomatic spinal stenosis.

In 1991, Herkowitz and Kurz published a prospective trial comparing decompression with decompression and intertransverse process arthrodesis in patients with degenerative SL with spinal stenosis [46]. In their cohort (36 females, 14 males), the results with regard to pain relief in the back and lower limbs were significantly better after a follow-up period of 3 years in the patients who received decompression with arthrodesis. However, since fusion with instrumentation is more common nowadays than fusion without, studies that only include fusion without instrumentation were also not included in the present analysis.

It needs to be emphasized that most of the cited studies were performed without nowadays knowledge of sagittal balance. Current and future studies will consider these fundamental parameters and therefore might lead to clearer results and conclusions.

In view of the clinical impact and importance of the pathological conditions concerned, the state of the medical literature capable of meeting the inclusion criteria for this study must be regarded as poor or even dreadful: there is a very strong need for more data. Considering the poverty of the data, the way in which the performance of surgery for these conditions is taken for granted in quite high numbers of patients can be regarded as disastrous.

Conclusions

- The number of controlled trials that address the key questions is very small, particularly in view of the large

numbers of operations carried out for the pathologies concerned.

- In adults with isthmic SL, surgery appears to be better in relation to pain and function than conservative treatment (poor evidence).
- In adults with degenerative SL, surgery appears to be better in relation to pain and function than conservative treatment (good evidence).
- In adults with degenerative SL and spinal stenosis, instrumented fusion with decompression appears to be more successful in relation to pain and function than decompression alone (poor evidence).
- In adults with isthmic or degenerative SL, reduction and instrumented fusion does not appear to be more successful in relation to pain and function than instrumented fusion without reduction (moderate evidence).

Compliance with ethical standards

Conflict of interest None.

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