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Review Article

Twenty-year perspective of randomized controlled trials for surgery of chronic nonspecific low back pain: citation bias and tangential knowledge

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Abstract

BACKGROUND CONTEXT: After decades of clinical research, the role of surgery for chronic nonspecific low back pain (CNLBP) remains equivocal. Despite significant intellectual, human, and economic investments into randomized controlled trials (RCTs) in the past two decades, the role of surgery in the treatment for CNLBP has not been clarified.

PURPOSE: To delineate the historical research agenda of surgical RCTs for CNLBP performed between 1993 and 2012 investigating whether conclusions from earlier published trials influenced the choice of research questions of subsequent RCTs on elucidating the role of surgery in the management of CNLBP.

STUDY DESIGN: Literature review.

METHODS: We searched the literature for all RCTs involving surgery for CNLBP. We reviewed relevant studies to identify the study question, comparator arms, and sample size. Randomized controlled trials were classified as ''indication'' trials if they evaluated the effectiveness of surgical therapy versus nonoperative care or as ''technical'' if they compared different surgical techniques, adjuncts, or procedures. We used citation analysis to determine the impact of trials on subsequent research in the field.

RESULTS: Altogether 33 technical RCTs (3,790 patients) and 6 indication RCTs (981 patients) have been performed. Since 2007, despite the unclear benefits of surgery reported by the first four indication trials published in 2001 to 2006, technical trials have continued to predominate (16 vs. 2). Of the technical trials, types of instrumentation (13 trials, 1,332 patients), bone graft materials and substitutes (11 trials, 833 patients), and disc arthroplasty versus fusion (5 trials, 1,337 patients) were the most common comparisons made. Surgeon authors have predominantly cited one of the indication trials that reported more favorable results for surgery, despite a lack of superior methodology or sample size. Trials evaluating bone morphogenic protein, instrumentation, and disc arthroplasty were all cited more frequently than the largest trial of surgical versus nonsurgical therapy.

CONCLUSIONS: The research agenda of RCTs for surgery of CNLBP has not changed substantially in the last 20 years. Technical trials evaluating nuances of surgical techniques significantly predominate. Despite the publication of four RCTs reporting equivocal benefits of surgery for CNLBP between 2001 and 2006, there was no change in the research agenda of subsequent RCTs, and technical trials continued to outnumber indication trials. Rather than clarifying what, if any, indications for surgery exist, investigators in the field continue to analyze variations in surgical technique, which will probably have relatively little impact on patient outcomes. As a result, clinicians unfortunately have little evidence to advise patients regarding surgical intervention for CNLBP.

Keywords: Lumbar fusion; Chronic nonspecific low back pain; Evidence-based medicine; Clinical trials; Citation bias

FDA device/drug status: Approved (lumbar instrumentation, bone morphogenic protein, disc arthroplasty).

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Introduction

The validity and benefit of clinical research depend on addressing questions that need to be answered. Generation of evidence depends on investigators' decisions about patient population, outcomes, and comparator arms. Ideally, such decisions are made rationally, after systematic review of evidence from previous experimentation [1,2], although there are numerous examples to suggest that such analysis is not undertaken, and potentially unnecessary trials are performed [3,4]. Trial funding sources may lead to systematic avoidance of potentially valuable head-to-head comparisons of proven therapies [5–7]. Conversely, much of medicine relies on historical tradition, rather than rigorous experimentation, and randomized controlled trial (RCT) evidence of treatment effectiveness, even for the most frequently performed interventions, is often still lacking. Such accepted, but unproven, medical practices are frequently reversed when subjected to rigorous testing [8]; therefore, evaluation of such popular practices is desirable from a societal perspective. It has been suggested that the reluctance of practitioners to test the fundamental effectiveness of their specialty's treatments might limit the generation of evidence on such topics [9] and lead to the generation of ''tangential'' evidence [10].

Chronic nonspecific low back pain (CNLBP) has been defined as ''LBP persisting for at least 12 weeks, not attributable to a recognizable, known specific pathology (eg, infection, tumor, osteoporosis, fracture, structural deformity, inflammatory disorder [eg, ankylosing spondylitis], radicular syndrome, or cauda equina syndrome)'' [11]. The frequency and cost of diagnostic imaging and medical and surgical therapies for this condition have risen dramatically in recent decades, without a commensurate improvement in population measures of outcome [12,13].

Surgical interventions, including fusion and disc arthroplasty, have been applied with the belief that abnormal intersegmental movement or degenerative pathology may be the cause of CNLBP. However, diagnostic criteria are variable [14], and lumbar degenerative changes are prevalent in the asymptomatic population [15], making the validity of this pathophysiologic concept uncertain. Rates of lumbar fusion vary dramatically within the United States and among countries, underscoring the uncertain indications for surgery in current clinical practice [16,17]. Four RCTs published between 2001 and 2006 compared lumbar fusion with nonoperative care [18–21]. Based on these results, recent systematic reviews and clinical guidelines have indicated a limited role for lumbar fusion in the treatment for CNLBP [11,22,23].

The tenets of evidence-based medical practice would predict that these results would temper enthusiasm for and reduce performance of surgery for CNLBP. On the contrary, lumbar fusion has been one of the most rapidly growing, commonly performed, and costly surgical procedures in the United States, despite the absence of new indications [24,25]. In light of this apparent lack of influence of previous trials on clinical practice, we sought to determine the effects of these trials on the subsequent research agenda on this topic.

Methods

We searched for trials published in English indexed in PubMed and Web of Science (last search September 2012) with the search strategy ''lumbar fusion'' OR ''back pain surgery'' OR ''lumbar instrument*'' OR ''disc degen*.'' We also searched ''clinicaltrials.gov'' and other databases to identify unpublished or ongoing clinical trials. We included RCTs that involved patients with CNLBP and included a surgical intervention as a comparator arm. We manually reviewed each article and excluded trials limited to patients with spondylolisthesis or scoliosis. We also checked the citation lists of systemic reviews and meta-analyses on the same topics to make sure that all relevant trials were included.

For each article, we recorded information on the authors, year, journal, comparator arms, and sample size of the trial. As a measure of recent relevance, we recorded the number of times that publications from 2010 to 2011 (the most recent two complete years before investigation) cited the trials or their follow-up publications. We categorized trials comparing surgical versus nonsurgical therapies as ''indication'' trials and those comparing different surgical techniques, approaches, or adjuncts as ''technical'' trials.

Because the first four indication trials published in 2001 to 2006 [18–21] reported uncertain benefits of surgery, we analyzed the number of indication and technical trials published after 2006 to see what influence these trials had on subsequent clinical research. We also used Web of Knowledge to analyze citation frequency as a measure of the relative impact of the indication trials in particular. Given the different years of publication, and thus the amount of time available to accrue citations, we analyzed citations made after January 2007, by which time these indication trials had been published. We categorized the affiliation of citing authors: if the primary or senior author of the citing publication had primary affiliation with a neurosurgery or orthopedic surgery department, we considered the publication to have a ''surgeon author.'' We also analyzed how subsequent CNLBP surgical trials—published since January 2007—cited these initial four indication trials. Two investigators performed all data extraction separately (NSA and JPF), which was then checked by another investigator (VB). The study had no outside funding.

Results

Altogether 39 RCTs were published involving surgery for CNLBP [18–21,26–60] (Table). From these 39 RCTs, 6 trials compared operative versus nonoperative treatments for CNLBP (indication trials) and 33 RCTs compared

Table
RCTs involving surgery for CNLBP

Study	Year	No. of patients	Intervention	No. of citations in 2010 and 2011
Zdeblick [26]	1993	124	Instrumentation	32
Thomsen et al. [27]	1997	130	Instrumentation	24
France et al. [28]	1999	71	Instrumentation	11
Diedrich et al. [29]	2001	40	Instrumentation	3
Fritzell et al. [18]	2001	294	Nonoperative versus surgery	84
Burkus et al. [30]	2002	279	Graft	77
Burkus et al. [31]	2002	46	Graft	35
Gibson et al. [32]	2002	69	Graft	9
Fritzell et al. [33]	2002	211	Instrumentation	67
Christensen et al. [34]	2002	148	Instrumentation	35
Madan et al. [35]	2003	55	Instrumentation	2
Brox et al. [19]	2003	64	Nonoperative versus surgery	44
Haid et al. [36]	2004	67	Graft	36
Sasso et al. [37]	2004	140	Instrumentation	9
Blumenthal et al. [38]	2005	304	Arthroplasty	185
Korovessis et al. [39]	2005	57	Graft	3
McKenna et al. [40]	2005	80	Instrumentation	8
Fairbank et al. [20]	2005	349	Nonoperative versus surgery	44
Jenis et al. [41]	2006	37	Graft	11
Kim et al. [42]	2006	167	Instrumentation	22
Brox et al. [21]	2006	60	Nonoperative versus surgery	25
Zigler et al. [43]	2007	237	Arthroplasty	50
Sasso et al. [44]	2008	67	Arthroplasty	7
Yee et al. [45]	2008	72	Device	2
Glassman et al. [46]	2008	102	Graft	23
Dai et al. [47]	2008	62	Graft	11
Putzier et al. [48]	2008	24	Graft	5
Berg et al. [49]	2009	152	Arthroplasty	14
Andersen et al. [50]	2009	107	Device	4
Thalgott et al. [51]	2009	50	Graft	4
Jiya et al. [52]	2009	26	Instrumentation	7
Rodríguez-Vela et al. [53]	2009	30	MIS	5
Gornet et al. [54]	2011	577	Arthroplasty	0
Sys et al. [55]	2011	40	Graft	0
Wang et al. [56]	2011	79	MIS	0
Hellum et al. [57]	2011	173	Nonoperative versus surgery	4
Ohtori et al. [58]	2011	41	Nonoperative versus surgery	2
Ringel et al. [59]	2012	60	Instrumentation	0
Xue et al. [60]	2012	80	Instrumentation	0

RCT, randomized controlled trial; CNLBP, chronic nonspecific low back pain; Instrumentation, evaluating different methods of fusion; arthroplasty, comparing disc arthroplasty and fusion; device, evaluating the use of an external device (eg, brace, bone stimulator); graft, evaluating the use of various bone grafts or bone morphogenic protein; MIS, evaluating minimally invasive techniques; nonoperative versus surgery, comparing surgical to nonoperative therapy.

variations of surgical techniques (technical trials) (Fig. 1). We did not detect any change in the research agenda after the publication of the first four indication trials published in 2001 to 2006. Despite that these first four indication trials showed uncertain benefits of surgery, in the following years from 2007 to 2012, technical trials have continued to be more frequent than indications trials (16 vs. 2) (Fig. 1). Of enrolled total 4,771 patients, 981 patients participated in indication trials, whereas technical trials enrolled 3,790 patients (Fig. 2). Of the technical trials, types of instrumentation (13 trials, 1,332 patients), bone graft materials and substitutes (11 trials, 833 patients), and disc arthroplasty versus fusion (5 trials, 1,337 patients) were the most common comparisons made.

The Table reports the combined citation counts arising in 2010 to 2011 for all publications (primary or follow-up reports) from a particular trial. Trials evaluating the use of bone morphogenic protein [31,32], instrumentation [33], and disc arthroplasty [38,43,61] were all cited more frequently than the largest indication trial [20] comparing surgical to nonsurgical care (Table). From 2007 to the present, the study of Fritzell et al. [18] was the most frequently cited indication trial. In particular, surgeon authors disproportionately cited this study more frequently than other trials, whereas nonsurgeon authors did not appear to have any strong preference (Fig. 3). Also the 16 technical trials preferentially cited Fritzell et al. [18] over any of the other indication trials (5 vs. 0).

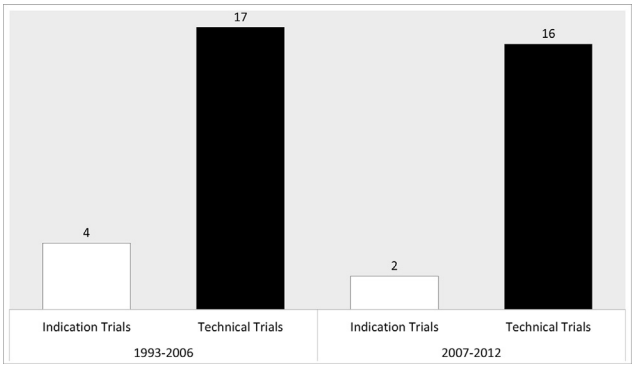

Fig. 1. Randomized controlled trials (RCTs) involving surgery for chronic nonspecific low back pain (CNLBP). From 39 RCTs, 6 trials compared operative versus nonoperative treatments for CNLBP (indication trials) and 33 RCTs compared variations of surgical techniques (technical trials). Between 1993 and 2006, four indication trials have been published showing uncertain benefits of surgery. In the following years 2007 to 2012, despite the ambiguous role of surgery in the management of CNLBP, technical trials have continued to be more frequent than indications trials.

Discussion

We analyzed the research agenda with respect to surgery for CNLBP. We note that there have been 39 RCTs involving lumbar fusion; yet, the vast majority has avoided a fundamental, and still controversial, question: is surgery superior to nonoperative management? Patient selection has been repeatedly cited as a reason for poor surgical results; yet, there is no consensus regarding appropriate diagnostic workup or precise indications for surgery [14]. In the meantime, a plethora of trials have investigated technical nuances, and large trials to introduce disc replacement have primarily compared it with fusion. It seems possible that, as has been recently demonstrated with several popular interventions [62–65], neither procedure has benefits beyond sham effects.

Randomized controlled clinical trials represent the highest level of evidence in clinical research. However, the practical value of a trial depends not only on its methods but also on the relevance of the question that it attempts to answer. Given that it is unclear who, if anyone, with CNLBP should undergo surgery, defining surgical indications would seem to be the most pressing subject for further trials, and further trials evaluating technical variations are of limited value in this setting. In agreeing to submit a major life decision (ie, surgery) to random chance, patients make an immense sacrifice and face considerable psychological uncertainty. Investigators undertaking indication trials have made admirable efforts to answer these difficult questions. Hence, it befits all involved to pay particular attention to these trials. However, it appears that results of these trials are often either overlooked or cited selectively. Spine surgeons, in particular, appear prone to disproportionately citing one trial with favorable results, despite a lack of methodological superiority or difference in sample size [22]. Furthermore, surgeon authors of technical trials cite disproportionately preexisting indication trials when reporting results of RCTs focused on comparing surgical techniques. This phenomenon has been shown to be present in other subspecialties as well, such as the preferences and avoidances in randomized trials of antifungal agents generating a potentially biased clinical research agenda [5]. Recent citation analysis suggests that, rather than being refuted or criticized, scientific findings inconsistent with a popular belief are simply ignored, as appears to be the case in this instance [66]. Other citation analyses indicate that positive findings [67] and publication in high-impact journals [68] make citation more likely.

We also noted that technical trials rarely mention uncertainty regarding surgical indications, one even going so far to say that lumbar fusion represented a ‘‘standard of care’’ for patients who had failed nonoperative treatments [44]. Some might argue that a discussion of operative indications is irrelevant in a trial of surgical techniques; however, if a surgery does not first prove to have patient benefit, then it is the technical variations that are irrelevant. Specialists’

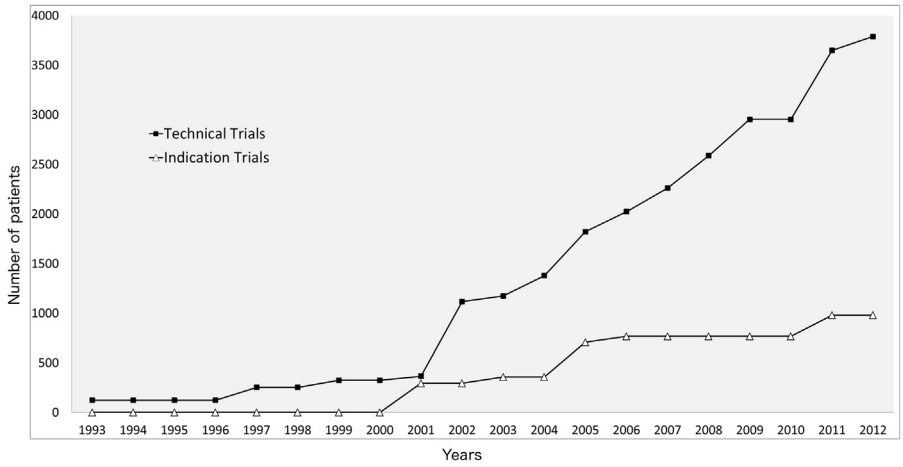

Fig. 2. Cumulative number of patients enrolled in indication versus technical trials. Of the total enrolled 4,771 patients, 981 patients participated in indication trials, whereas technical trials enrolled 3,790 patients.

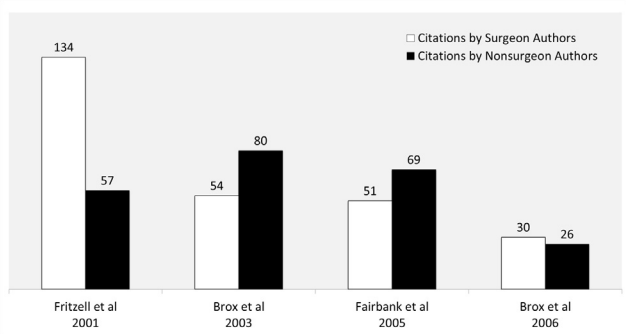

Fig. 3. Citation frequency of the first four indication trials published 2001 to 2006. Surgeon authors disproportionately cited the study of Fritzell et al. [18] more frequently than other trials, whereas nonsurgeon authors did not appear to have any strong preference.

objectivity in evaluating the effectiveness and appropriateness of procedures that they themselves perform has been a subject of interest [69–71].

It has also been noted that guidelines based on clinical research findings do not necessarily translate into practice [72], especially when such guidelines suggest the curtailment of procedures [73,74]. Investigators and drug or device companies have traditionally initiated most clinical trials, although in 2009, the US Institute of Medicine released a list of priority topics for comparative effectiveness research, with the evaluation of treatment strategies for LBP being among the highest [75]. It is notable that the major indication trials were government funded [18,20,57], whereas major US trials of disc arthroplasty and fusion adjuncts have been sponsored by device manufacturers [38,54]. It has been shown that funded trials publish positive results more frequently [76], a phenomenon identified as ''funding-driven bias'' [77]. Bartels et al. [78] investigated financial disclosures of authors involved in spine research and found that authors with disclosed financial relationships significantly less often published articles with neutral or negative conclusions. As in other fields of medicine [79–82], the influence of financial interests on research conclusions in spine surgery appears to be substantial.

The most significant limitation of our analysis is that we cannot know why some authors did or did not cite particular trials or why investigators chose to perform the trials that they did. Citations are a limited indication of a particular work's influence on subsequent authors' thoughts, motivations, and efforts. However, within the current system of scientific publication, it is the most readily available and explicit relationship of ideas and beliefs and has been the most widely used method for such bibliometric analysis. Publication bias may influence the availability of trial reports, although this has never been investigated specifically for spine surgery. The citation process may be subject to technical error [83,84], but the type and magnitude of error reported do not seem sufficient to influence results of our analysis. Also citation analysis only represents the opinions of published authors, a limited, albeit influential, fraction of all practitioners. A direct survey [14], or national discharge databases [17], might provide a broader sampling of surgeons' beliefs on this topic.

Conclusions

The research agenda of RCTs for surgery of CNLBP has not changed substantially in the last 20 years. Technical trials evaluating nuances of surgical techniques significantly predominate. Despite the publication of four RCTs reporting equivocal benefits of surgery for CNLBP between 2001 and 2006, there was no change in the research agenda of subsequent RCTs and technical trials continued to outnumber indication trials. Rather than clarifying what, if any, indications for surgery exist, investigators in the field continue to analyze variations in surgical technique, which will probably have relatively little impact on patient outcomes [78]. As a result, clinicians unfortunately have little evidence to advise patients regarding surgical intervention for CNLBP.

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References

[1] Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. J Clin Epidemiol 1995;48:45–57.
[2] Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. BMJ 2007;334:349–51.
[3] Lau J, Antman EM, Jimenez-Silva J, et al. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992;327:248–54.
[4] Robinson KA, Goodman SN. A systematic examination of the citation of prior research in reports of randomized, controlled trials. Ann Intern Med 2011;154:50–5.
[5] Rizos EC, Salanti G, Kontoyiannis DP, Ioannidis JP. Homophily and co-occurrence patterns shape randomized trials agendas: illustration in antifungal agents. J Clin Epidemiol 2011;64:830–42.
[6] Estellat C, Ravaud P. Lack of head-to-head trials and fair control arms: randomized controlled trials of biologic treatment for rheumatoid arthritis. Arch Intern Med 2012;172:237–44.
[7] Dunn AG, Bourgeois FT, Murthy S, et al. The role and impact of research agendas on the comparative-effectiveness research among antihyperlipidemics. Clin Pharmacol Ther 2012;91:685–91.
[8] Prasad V, Gall V, Cifu A. The frequency of medical reversal. Arch Intern Med 2011;171:1675–6.
[9] Prasad V, Cifu A, Ioannidis JP. Reversals of established medical practices: evidence to abandon ship. JAMA 2012;307:37–8.
[10] Puhan MA, Vollenweider D, Steurer J, et al. Where is the supporting evidence for treating mild to moderate chronic obstructive pulmonary disease exacerbations with antibiotics? A systematic review. BMC Med 2008;6:28.

[11] Airaksinen O, Brox JI, Cedraschi C, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. Eur Spine J 2006;15(2 Suppl):S192–300.
[12] Deyo RA, Mirza SK, Turner JA, Martin BI. Overtreating chronic back pain: time to back off? J Am Board Fam Med 2009;22:62–8.
[13] Deyo RA, Mirza SK. The case for restraint in spinal surgery: does quality management have a role to play? Eur Spine J 2009;18(3 Suppl):331–7.
[14] Willems PC, de Bie R, Oner C, et al. Clinical decision making in spinal fusion for chronic low back pain. Results of a nationwide survey among spine surgeons. BMJ Open 2011;1:e000391.
[15] Hicks GE, Morone N, Weiner DK. Degenerative lumbar disc and facet disease in older adults: prevalence and clinical correlates. Spine 2009;34:1301–6.
[16] Cherkin DC, Deyo RA, Loeser JD. An international comparison of back surgery rates. Spine 1994;19:1201–6.
[17] Weinstein JN, Lurie JD, Olson PR, et al. United States' trends and regional variations in lumbar spine surgery: 1992-2003. Spine 2006;31:2707–14.
[18] Fritzell P, Hagg O, Wessberg P, Nordwall A. 2001 Volvo Award Winner in Clinical Studies: lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. Spine 2001;26:2521–32.
[19] Brox JI, Sorensen R, Friis A, et al. Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. Spine 2003;28:1913–21.
[20] Fairbank J, Frost H, Wilson-MacDonald J, et al. Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. BMJ 2005;330:1233.
[21] Brox JI, Reikeras O, Nygaard O, et al. Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: a prospective randomized controlled study. Pain 2006;122:145–55.
[22] Mirza SK, Deyo RA. Systematic review of randomized trials comparing lumbar fusion surgery to nonoperative care for treatment of chronic back pain. Spine 2007;32:816–23.
[23] Chou R, Loeser JD, Owens DK, et al. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: an evidence-based clinical practice guideline from the American Pain Society. Spine 2009;34:1066–77.
[24] Deyo RA, Gray DT, Kreuter W, et al. United States trends in lumbar fusion surgery for degenerative conditions. Spine 2005;30:1441–5.
[25] Pumberger M, Chiu YL, Ma Y, et al. National in-hospital morbidity and mortality trends after lumbar fusion surgery between 1998 and 2008. J Bone Joint Surg Br 2012;94:359–64.
[26] Zdeblick TA. A prospective, randomized study of lumbar fusion. Preliminary results. Spine 1993;18:983–91.
[27] Thomsen K, Christensen FB, Eiskjaer SP, et al. 1997 Volvo Award winner in clinical studies. The effect of pedicle screw instrumentation on functional outcome and fusion rates in posterolateral lumbar spinal fusion: a prospective, randomized clinical study. Spine 1997;22:2813–22.
[28] France JC, Yaszemski MJ, Lauerman WC, et al. A randomized prospective study of posterolateral lumbar fusion. Outcomes with and without pedicle screw instrumentation. Spine 1999;24:553–60.
[29] Diedrich O, Perlick L, Schmittt O, Kraft CN. Radiographic spinal profile changes induced by cage design after posterior lumbar interbody fusion preliminary report of a study with wedged implants. Spine 2001;26:E274–80.
[30] Burkus JK, Cornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech 2002;15:337–49.
[31] Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. Spine 2002;27:2396–408.
[32] Gibson S, McLeod I, Wardlaw D, Urbaniak S. Allograft versus autograft in instrumented posterolateral lumbar spinal fusion: a randomized control trial. Spine 2002;27:1599–603.
[33] Fritzell P, Hagg O, Wessberg P, Nordwall A. Chronic low back pain and fusion: a comparison of three surgical techniques: a prospective multicenter randomized study from the Swedish lumbar spine study group. Spine 2002;27:1131–41.
[34] Christensen FB, Hansen ES, Eiskjaer SP, et al. Circumferential lumbar spinal fusion with Brantigan cage versus posterolateral fusion with titanium Cotrel-Dubousset instrumentation: a prospective, randomized clinical study of 146 patients. Spine 2002;27:2674–83.
[35] Madan S, Boeree NR. Outcome of the Graf ligamentoplasty procedure compared with anterior lumbar interbody fusion with the Hartshill horseshoe cage. Eur Spine J 2003;12:361–8.
[36] Haid RW, Branch CL, Alexander JT, Burkus K. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. Spine J 2004;4:527–38.
[37] Sasso RC, Kitchel SH, Dawson EG. A prospective, randomized controlled clinical trial of anterior lumbar interbody fusion using a titanium cylindrical threaded fusion device. Spine 2004;29:113–22.
[38] Blumenthal S, McAfee PC, Guyer RD, et al. A prospective, randomized, multicenter Food and Drug Administration investigational device exemptions study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: part I: evaluation of clinical outcomes. Spine 2005;30:1565–75.
[39] Korovessis P, Koureas G, Zacharatos S, et al. Correlative radiological, self-assessment and clinical analysis of evolution in instrumented dorsal and lateral fusion for degenerative lumbar spine disease. Autograft versus coralline hydroxyapatite. Eur Spine J 2005;14:630–8.
[40] McKenna PJ, Freeman BJC, Mulholland RC, et al. A prospective, randomised controlled trial of femoral ring allograft versus a titanium cage in circumferential lumbar spinal fusion with minimum 2-year clinical results. Eur Spine J 2005;14:727–37.
[41] Jenis LG, Banco RJ, Kwon B. A prospective study of Autologous Growth Factors (AGF) in lumbar interbody fusion. Spine J 2006;6:14–20.
[42] Kim KT, Lee SH, Lee YH, et al. Clinical outcomes of 3 fusion methods through the posterior approach in the lumbar spine. Spine 2006;31:1351–7.
[43] Zigler J, Delamarter R, Spivak JM, et al. Results of the prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential fusion for the treatment of 1-level degenerative disc disease. Spine 2007;32:1155–62.
[44] Sasso RC, Foulk DM, Hahn M. Prospective, randomized trial of metal-on-metal artificial lumbar disc replacement: initial results for treatment of discogenic pain. Spine 2008;33:123–31.
[45] Yee AJ, Yoo JU, Marsolais EB, et al. Use of a postoperative lumbar corset after lumbar spinal arthrodesis for degenerative conditions of the spine. A prospective randomized trial. J Bone Joint Surg Am 2008;90:2062–8.
[46] Glassman SD, Carreon LY, Djurasovic M, et al. RhBMP-2 versus iliac crest bone graft for lumbar spine fusion: a randomized, controlled trial in patients over sixty years of age. Spine 2008;33:2843–9.
[47] Dai LY, Jiang LS. Single-level instrumented posterolateral fusion of lumbar spine with beta-tricalcium phosphate versus autograft: a prospective, randomized study with 3-year follow-up. Spine 2008;33:1299–304.

[48] Putzier M, Strube P, Funk J, et al. Periosteal cells compared with autologous cancellous bone in lumbar segmental fusion. J Neurosurg Spine 2008;8:536–43.
[49] Berg S, Tullberg T, Branth B, et al. Total disc replacement compared to lumbar fusion: a randomised controlled trial with 2-year follow-up. Eur Spine J 2009;18:1512–9.
[50] Andersen T, Christensen FB, Ernst C, et al. The effect of electrical stimulation on lumbar spinal fusion in older patients: a randomized, controlled, multi-center trial: part 1: functional outcome. Spine 2009;34:2241–7.
[51] Thalgott JS, Fogarty ME, Giuffre JM, et al. A prospective, randomized, blinded, single-site study to evaluate the clinical and radiographic differences between frozen and freeze-dried allograft when used as part of a circumferential anterior lumbar interbody fusion procedure. Spine 2009;34:1251–6.
[52] Jiya TU, Smit T, van Royen BJ, Mullender M. Posterior lumbar interbody fusion using non resorbable poly-ether-ether-ketone versus resorbable poly-L-lactide-co-D,L-lactide fusion devices. Clinical outcome at a minimum of 2-year follow-up. Eur Spine J 2011;20:618–22.
[53] Rodriguez-Vela J, Lobo-Escolar A, Joven-Aliaga E, et al. Perioperative and short-term advantages of mini-open approach for lumbar spinal fusion. Eur Spine J 2009;18:1194–201.
[54] Gornet MF, Burkus JK, Dryer RF, Peloza JH. Lumbar disc arthroplasty with Maverick disc versus stand-alone interbody fusion: a prospective, randomized, controlled, multicenter investigational device exemption trial. Spine 2011;36:E1600–11.
[55] Sys J, Weyler J, Van der Zijden T, et al. Platelet-rich plasma in mono-segmental posterior lumbar interbody fusion. Eur Spine J 2011;20:1650–7.
[56] Wang HL, Lu FZ, Jiang JY, et al. Minimally invasive lumbar interbody fusion via MAST Quadrant retractor versus open surgery: a prospective randomized clinical trial. Chin Med J (Engl) 2011;124:3868–74.
[57] Hellum C, Johnsen LG, Storheim K, et al. Surgery with disc prosthesis versus rehabilitation in patients with low back pain and degenerative disc: two year follow-up of randomised study. BMJ 2011;342:d2786.
[58] Ohtori S, Koshi T, Yamashita M, et al. Surgical versus nonsurgical treatment of selected patients with discogenic low back pain: a small-sized randomized trial. Spine 2011;36:347–54.
[59] Ringel F, Stuer C, Reinke A, et al. Accuracy of robot-assisted placement of lumbar and sacral pedicle screws a prospective randomized comparison to conventional freehand screw implantation. Spine 2012;37:E496–501.
[60] Xue H, Tu Y, Cai M. Comparison of unilateral versus bilateral instrumented transforaminal lumbar interbody fusion in degenerative lumbar diseases. Spine J 2012;12:209–15.
[61] Guyer RD, McAfee PC, Banco RJ, et al. Prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: five-year follow-up. Spine J 2009;9:374–86.
[62] Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347:81–8.
[63] Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med 2009;361:557–68.
[64] Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med 2009;361:569–79.
[65] Iversen T, Solberg TK, Romner B, et al. Effect of caudal epidural steroid or saline injection in chronic lumbar radiculopathy: multicentre, blinded, randomised controlled trial. BMJ 2011;343:d5278.
[66] Greenberg SA. How citation distortions create unfounded authority: analysis of a citation network. BMJ 2009;339:b2680.
[67] Kjaergard LL, Gluud C. Citation bias of hepato-biliary randomized clinical trials. J Clin Epidemiol 2002;55:407–10.
[68] Callaham M, Wears RL, Weber E. Journal prestige, publication bias, and other characteristics associated with citation of published studies in peer-reviewed journals. JAMA 2002;287:2847–50.
[69] Leape LL, Park RE, Kahan JP, Brook RH. Group judgments of appropriateness: the effect of panel composition. Qual Assur Health Care 1992;4:151–9.
[70] Coulter I, Adams A, Shekelle P. Impact of varying panel membership on ratings of appropriateness in consensus panels: a comparison of a multi- and single disciplinary panel. Health Serv Res 1995;30:577–91.
[71] Kahan JP, Park RE, Leape LL, et al. Variations by specialty in physician ratings of the appropriateness and necessity of indications for procedures. Med Care 1996;34:512–23.
[72] Deyell MW, Buller CE, Miller LH, et al. Impact of National Clinical Guideline recommendations for revascularization of persistently occluded infarct-related arteries on clinical practice in the United States. Arch Intern Med 2011;171:1636–43.
[73] Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.
[74] Lin GA, Dudley RA, Redberg RF. Cardiologists' use of percutaneous coronary interventions for stable coronary artery disease. Arch Intern Med 2007;167:1604–9.
[75] Kuehn BM. Institute of Medicine outlines priorities for comparative effectiveness research. JAMA 2009;302:936–7.
[76] Shah RV, Albert TJ, Bruegel-Sanchez V, et al. Industry support and correlation to study outcome for papers published in Spine. Spine 2005;30:1099–104.
[77] Rampton S, Stauber J. Research funding, conflicts of interest, and the meta-methodology of public relations. Public Health Rep 2002;117:331–9.
[78] Bartels RH, Delye H, Boogaarts J. Financial disclosures of authors involved in spine research: an underestimated source of bias. Eur Spine J 2012;21:1229–33.
[79] Irwin RS. The role of conflict of interest in reporting of scientific information. Chest 2009;136:253–9.
[80] Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA 2003;289:454–65.
[81] Morin K, Rakatansky H, Riddick FA Jr, et al. Managing conflicts of interest in the conduct of clinical trials. JAMA 2002;287:78–84.
[82] Lexchin J, Bero LA, Djulbergovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 2003;326:1167–70.
[83] Aronsky D, Ransom J, Robinson K. Accuracy of references in five biomedical informatics journals. J Am Med Inform Assoc 2005;12:225–8.
[84] Unver B, Senduran M, Unver Kocak F, et al. Reference accuracy in four rehabilitation journals. Clin Rehabil 2009;23:741–5.