Heliyon 7 (2021) e07286

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

# Effects of adhesion barrier gel on functional outcomes of patients with lumbar disc herniation surgery; A systematic review and meta-analysis of clinical trials

Seyedmorteza Hosseini [a], Amin Niakan [b], Maryam Dehghankhalili [c], Reza Dehdab [a], Shima Shahjouei [d], Yasamin Rekabdar [e], Elaheh Shaghaghian [f], Alireza Shaghaghian [g], Fariborz Ghaffarpasand [a,*]

[a] Research Center for Neuromodulation and Pain, Shiraz University of Medical Sciences, Shiraz, Iran
[b] Trauma Research Center, Department of Neurosurgery, Shiraz University of Medical Sciences, Shiraz, Iran
[c] Department of General Surgery, Shiraz University of Medical Sciences, Shiraz, Iran
[d] Neuroscience Institute, Geisinger Health System, Pennsylvania, USA
[e] Young Researchers and Elite Club, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran
[f] Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
[g] Kowsar Hospital, Shiraz, Iran

ARTICLE INFO

*Keywords:*
Adhesion barrier gel
Functional outcome
Lumbar disc surgery
Meta-analysis

ABSTRACT

Failed Back Surgery Syndrome (FBSS) is persistent pain and disability following lumbar laminectomy which is associated with decreased quality of life and disability and has been reported in up to 40% of the patients undergoing lumbar laminectomy. Several approaches have been introduced to reduce the rate of the FBSS. Among these, applying anti-adhesive barrier gels have been studied with interest with controversial results. The aim of the current study was to determine the effects of anti-adhesive barrier gels on functional outcome and recurrence of patients undergoing lumbar disc surgery. We searched databases including EMBASE, PUBMED, Web of Science, Scopus, Cochrane Library, and scholar databases until November 2019. To assess the heterogeneity across included studies was used Cochran's Q and I-square ($I^2$) statistics. Standardized mean difference (SMD) and 95% CI between were used to estimate pooled effect sizes. Out of 4507, 10 clinical trials found to be appropriate for current meta-analysis. The pooled results of included clinical trials indicated that adhesion barrier gel significantly decreased leg pain (LP) (SMD = −0.31; 95% CI, −0.60, −0.03; P = 0.032; $I^2$: 59.2%) among patients with lumbar disc herniation surgery. Back pain (BP) (SMD = −0.03; 95% CI, −0.23, 0.16; P = 0.734; $I^2$: 40.2%), and Oswestry disability index (ODI) (SMD = −0.11; 95% CI, −0.27, 0.05; P = 0.178; $I^2$: 0.0%), were not significantly affected following adhesion barrier gel application. Application of adhesion barrier gel in single level lumbar disc surgery is associated with deceased leg pain. However, its application does not affect the low back pain, disability and gate. Further, larger randomized clinical trials are required.

## 1. Introduction

Low back pain (LBP), is a major public health problem in both developed and developing countries which is associated with high social and economic burden with estimated worldwide prevalence of 22% in general population [1, 2]. More than half of the patients with LBP suffer from lumber intervertebral disc (IVD) pathologies and herniation which requires treatment [3, 4]. The treatment of the LBP and IVD-attributable pain, is based on the duration of symptoms, the clinical examination, neurological status and imaging findings and is consisted of life-style modifications, medical and physical therapies and finally surgery [5]. Although genetic factors play an important role in pathogenesis of LBP and IVD pathologies [6, 7], but the natural course of the disease remain elusive and requires interventions mostly [8, 9]. This places the spine surgical procedures and mostly the lumbar laminectomy among the most common procedures performed for treatment of the radiculopathy and LBP [3, 4]. The aim of the lumbar laminectomy is the decompression of the neural elements and restring the normal anatomical borders of the

* Corresponding author.
*E-mail address:* fariborz.ghaffarpasand@gmail.com (F. Ghaffarpasand).

https://doi.org/10.1016/j.heliyon.2021.e07286
Received 21 December 2020; Received in revised form 21 March 2021; Accepted 7 June 2021

intervertebral foramens and the spinal canal, to avoid further neurologic injury and alleviating radicular pain.

Failed Back Surgery Syndrome (FBSS) is persistent pain and disability following lumbar laminectomy which is associated with decreased quality of life and disability and has been reported in up to 40% of the patients undergoing lumbar laminectomy [10, 11]. The pathophysiology is currently under investigations, but the three-dimensional (3D) adhesion theory explain the phenomenon as fibrosis surrounding the epidural tissues secondary to the injured sacrospinalis behind, fibrous rings and posterior longitudinal ligaments [10]. Other risk factors of FBSS include residual stenosis, dural tear, nerve damage (preoperative or intraoperative), incomplete recovery, poor musculature, excessive weight or post laminectomy instability [11]. In addition, the rate of recurrent disc herniation and radiculopathy following minimally invasive and open procedures has been reported to vary between 3.6 to 14.8% in different series [12, 13]. Several approaches and interventions have been introduced and examined to decrease the rate of FBSS, recurrent disc herniation and radiculopathy following lumbar laminectomy which include minimal invasive techniques [14], medical therapies [15], application of biomaterials [16] and intraoperative use of adhesive barrier gels [17, 18]; however, the results are controversial. Among these approaches, a great interest has been paid to intraoperative application of biomaterials that refer to absorbable anti-adhesive barrier gels [19, 20]. Several products have been introduced by now which are cellulose-based and follow the same instruction of use and the same mechanism of action: to provide a barrier gel between the dura matter and the paravertebral muscles and in return, preventing adhesion between these issues and avoiding secondary compression of the neural elements [20]. As the clinical results following application of these barrier gels are confusing, we conducted this systematic review and meta-analysis of the randomized clinical trials to determine the effects of anti-adhesive barrier gels on functional outcome and recurrence of patients undergoing lumbar disc surgery.

## 2. Materials and methods

### 2.1. Search strategy

We conducted a comprehensive search in electronic databases including Embase, PubMed, Web of Science, Scopus, Cochrane Library databases and Google Scholar until January 2020 by combining MeSH and text keywords. The following search pattern was used: [Keywords for adhesion barrier gel] AND [Keywords related to functional outcomes OR lumbar disc herniation surgery]. Searches were limited to clinical trials that have investigated the effect of adhesion barrier gel on functional outcomes in humans and studies published in English. And also, we manually checked the reference lists of included clinical trials and previous reviews to catch additional studies.

### 2.2. Selection criteria

The eligible studies were required to meet certain criteria: 1) the original study was a clinical trial either with randomized or non-randomized design, 2) human clinical trials with patients undergoing lumbar discectomy 3) the intervention group received any form of adhesion barrier gels, whereas the comparison group received an active comparator or placebo, 4) studies that reported appropriate data (means, standard deviations (SDs), standard error of the mean (SEMs), or related 95% confidence intervals (CIs) to calculate the mean changes on outcomes including leg pain (LP), back pain (BP), Oswestry disability index (ODI), and radiculopathy score (RS) between intervention and comparison groups, 5) studies that have performed one- or two-level laminectomy or laminotomy along with discectomy. Animal clinical trials, in vitro studies, case reports, letters, observational studies, data from posters/abstracts without full texts, and studies were not control group were excluded from current meta-analysis. We have also excluded those studies which performed minimally-invasive spinal surgery, those with microscopic approaches and those who performed spinal instrumentation.

### 2.3. Data extraction and quality assessment

Data extraction was conducted independently by two authors using a standard Excel sheet. The following data was extracted: first author, year of publication, study location, study population, age group (control group and intervention group), study design, type of intervention and placebo, sample size in intervention and comparison groups, dosage and duration of intervention, means and SDs/or related 95% CIs for LP, BP, ODI, and RS in both groups. The RS is a combination of LP and physical examination. On a four-point scale (never, occasionally, frequently, and always) patients indicated how often they had experienced the following symptoms during the last 7 days: 1) numbness or tingling in the lower extremities; 2) weakness in the lower extremities; 3) bowel or bladder dysfunction; and 4) trouble falling asleep or being awakened from sleep by pain. Responses have been converted to numerical values ranging from 1 (never) to 4 (always), and then combined and rescaled to yield physical symptoms scores from 0 to 100. A RS has been obtained by summing the leg pain severity scores and the symptoms scores, and then dividing by 2 [17, 21, 22, 23]. The quality assessment of selected clinical trials was performed using Cochrane risk of bias tool according risk of bias items including: "random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting" [24].

### 2.4. Statistical analysis

All met-analyses were performed using STATA software version 12.0 (Stata Corp., College Station, TX) and RevMan V.5.3 software (Cochrane Collaboration, Oxford, UK). The pooled findings of included clinical trials are considered as standardized mean differences (SMDs) with 95% CIs. The heterogeneity across included clinical trials was examined using Cochran's Q test and I2 test. A $P < 0.05$ with I2 more than 50% is indicated a significant evidence of heterogeneity existence across included clinical trials. Based on the differences between included studies for the pooling model was used a random-effects model with Hedges statistic. Additional analyses including subgroup- and sensitivity analyses were conducted. Subgroup analyses were performed based on variables such as name of outcomes (LSOQ score vs. VAS score), type of intervention (ADCON-L gel vs. oxiplex gel vs. others) and duration of intervention ($\leq$6 months vs. $>$ 6 months). Sensitivity analyses were used to examine the effect of each trial on the validity of the pooled SMDs using leave-one-out method. The publication bias across included studies was assessed using Egger's regression- and Begg's-tests. P values $< 0.05$ were considered as statistically significant.

## 3. Results

About, 4757 citations were initially identified in comprehensive online searches. After excluded duplicates and screened based on titles and abstracts, and then removed non-related citations, 10 clinical trials (12 trials) were finally selected to be eligible for current meta-analysis [17, 18, 21, 22, 23, 25, 26, 27, 28, 29]. The process of clinical trials identification and selection are shown in Figure 1. All 10 included articles were randomized controlled trials. Total sample sizes were 1002 (456 in control group and 546 in intervention group) and in each included clinical trial varied from 18 to 357 participants. Nine trials estimated the effects of adhesion barrier gel on LP, six on BP and ODI, and five on RP [17, 18, 21, 22, 23, 25, 26, 27, 28, 29]. The selected trials have been published from 2001 to 2018. Fransen *et al.* [25], study did not specify that visual analog scale (VAS) score was for which outcome, so we considered VAS score for leg pain's outcome. The ODI was reported as a value of 0–50 in some studies and as a reduction percentage in some

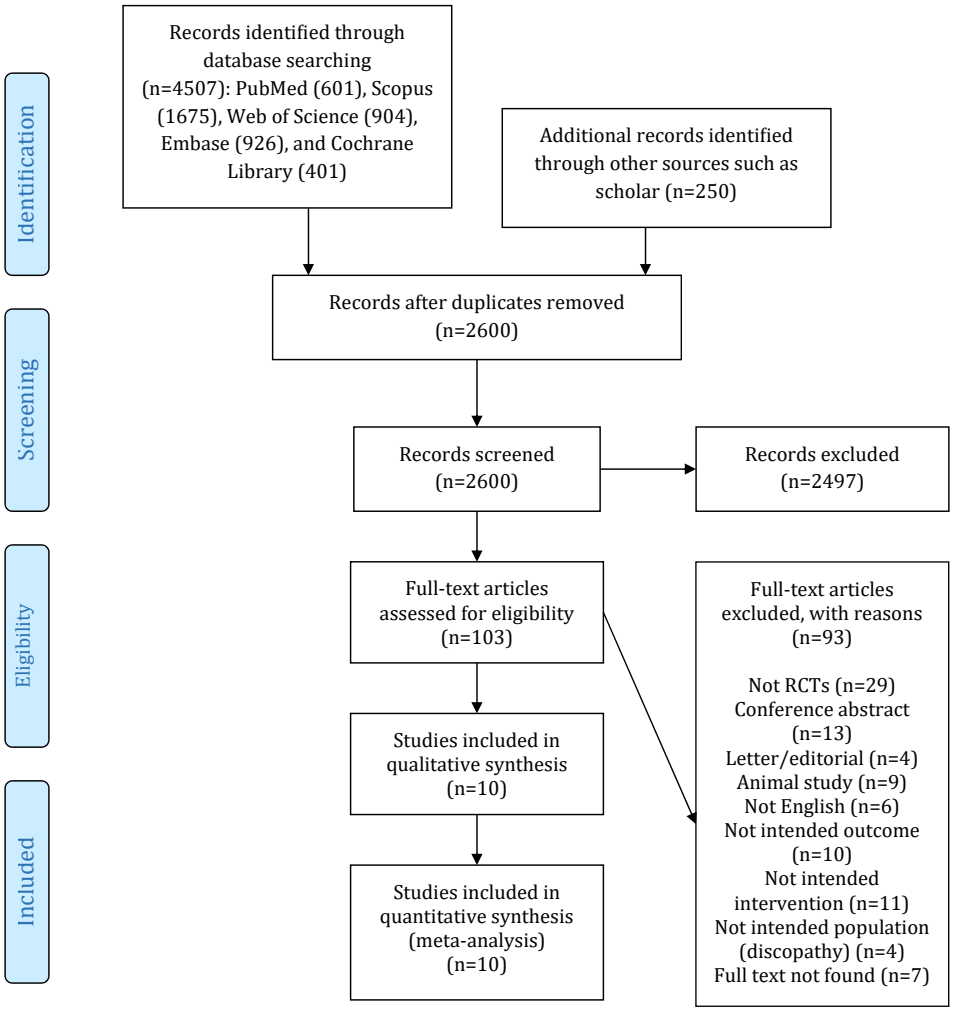


**Figure 1.** Literature search and review flowchart for selection of studies.

others. We have uniformed all the ODI scores accordingly. The detailed characteristics of included trials are presented in Table 1.

### 3.1. Main outcomes

Forest plots showing the effects of adhesion barrier gel on LP, BP, and ODI, are presented in Figure 2. The pooled results of included clinical trials indicated that adhesion barrier gel significantly decreased LP (SMD = −0.31; 95% CI, −0.60, −0.03; P = 0.032; $I^2$: 59.2%) among patients with lumbar disc herniation surgery. BP (SMD = −0.03; 95% CI, −0.23, 0.16; P = 0.734; $I^2$: 40.2%), and ODI (SMD = −0.11; 95% CI, −0.27, 0.05; P = 0.178; $I^2$: 0.0%), did not significantly change following adhesion barrier gel use.

### 3.2. Subgroup and sensitivity analyses

Detailed meta-analysis results for the effects of adhesion barrier gel use on functional outcomes based on subgroup analyses findings have been summarized in Table 2. The findings of subgroup analyses showed that compared to studies with LSOQ score, following adhesion barrier gel use the pain of leg significantly decreased in studies with VAS score (−0.08 vs. −0.53, 95% CI: −0.86, −0.20, I2: 30.3%). The pooled data from trials with oxiplex gel showed significant decreased on LP vs. others use (−0.24 vs. −0.33, 95% CI: −0.65, −0.01, I2: 64.9%). With regard to duration of intervention, analysis of pooled data from studies indicated that adhesion barrier gel significantly decreased ODI in studies with >6 months duration of intervention (SMD = −0.42; 95% CI, −0.79, −0.04; $I^2$:0.0%) in compared with studies with ≤6 months. But the subgroup analyses for BP and RS were not significant.

Sensitivity analyses showed no significant differences between the before and after sensitivity pooled SMDs for BP, ODI, and RS. For LP, there was a significant differences between the before (SMD = −0.31; 95% CI, −0.60, −0.03) and after sensitivity pooled SMDs after excluding Lei et al. [26](SMD = −0.25; 95% CI, −0.53, 0.03), Assietti et al. [29] (SMD = −0.25; 95% CI, −0.55, 0.04), and Liu et al. [26](SMD = −0.29; 95% CI, −0.63, 0.03).

### 3.3. Publication bias and quality assessment

Egger and Begg's tests were applied to determine the evidence of publication bias in this meta-analysis. These statistics showed no significant publication bias for meta-analyses examining the impact of adhesion barrier gel on LP (P Egger's test = 0.63, P Begg's test = 0.84), BP (P Egger's test = 0.98, P Begg's test = 0.85), ODI (P Egger's test = 0.40, P Begg's test = 0.85), and RS (P Egger's test = 0.20, P Begg's test = 0.99). The methodological quality assessment of included clinical trials

**Table 1.** Characteristics of included primary Clinical trials.

| Authors (Ref) | Publication year | Sample size (control /intervention) | Country | Intervention (name and daily dose) | Schedule of supplementation intake (months) | Presented data | Age (y) (control, intervention) |
|---|---|---|---|---|---|---|---|
| Richter et al. [23] | 2001 | 177/180 | Germany | 3–5 gr ADCON-L gel | 6 | BP, ODI, RP | 42.9, 43.1 |
| Kim et al. [22] | 2003 | 12/23 | USA | 1–3 ml (~3 ml) Oxiplex/Sp gel | 6 | LP, ODI, RP | 43.6 ± 8.75, 43.5 ± 9.25 |
| Kim et al. [21] | 2004 | 7/11 | USA | 1–3 ml (~3 ml) Oxiplex/Sp gel | 12 | LP, ODI, RP | NR |
| Cengiz #1 et al. [17] | 2007 | 9/21 | Turkey | ~3 ml ADCON-L gel | 7.5 | RP | 39.77 ± 7.58, 47.33 ± 12.67 |
| Cengiz$_{\#2}$ et al. [17] | 2007 | 9/21 | Turkey | ~3 ml Healon GV | 7.5 | RP | 39.77 ± 7.58, 44.76 ± 11.57 |
| Assietti et al. [29] | 2008 | 35/35 | Italy | NR Carboxymethylcellulose/Polyethylene Oxide gel | 36 | LP, BP, and ODI | 57.1, 54.8 |
| Fransen et al. [25] | 2010 | 10/10 | Belgium | 1.3 mL DuraSeal Xact Adhesion Barrier and Sealant System (DSX) | 6 | LP | 38 ± 12, 41.4 ± 12.5 |
| Rhyne $_{\#1}$ et al. [28] | 2012 | 63/67 | USA | 1–3 ml (~3 ml) Oxiplex gel (carboxymethylcellulose, polyethylene oxide, and calcium) | 6 | LP, BP | 41.71 ± 10.66, 41.81 ± 10.53 |
| Rhyne $_{\#2}$ et al. [28] | 2012 | 78/78 | USA | 1–3 ml (~3 ml) Oxiplex gel (carboxymethylcellulose, polyethylene oxide, and calcium) | 6 | LP, BP | 41.71 ± 10.66, 41.81 ± 10.53 |
| Lei et al. [26] | 2013 | 13/20 | China | 1–3 ml (~3 ml) Oxiplex gel | 2 | LP | 38.86 ± 9.77, 40.10 ± 13.80 |
| Liu et al. [26] | 2013 | 33/60 | China | ~3 ml CMC/PEO gel (Carboxymethylcellulose/polyethylene oxide gel) | 2 | LP, BP, and ODI | 36.67 ± 11.98, 40.45 ± 13.92 |
| Shvets et al. [18] | 2018 | 10/20 | Russia | NR Antiadgezin gel | 12 | LP, BP, and ODI | NR |

* LP: Leg pain, BP: Back pain; ODI: Oswestry disability index; RP: Radicular pain; NR: Not reporting.

**Table 2.** The effects of adhesion barrier gel on functional outcomes with CI 95% between based on subgroup analysis.

| Variable | | Number of SMD included | Subgroups | Pooled effect estimate | 95% CI | $I^2$ (%) | Overall $I^2$ (%) |
|---|---|---|---|---|---|---|---|
| LP | Name of outcomes | 4 | LSOQ score | −0.08 | −0.49, 0.32 | 61.9 | 59.2 |
| | | 5 | VAS score | −0.53 | −0.86, −0.20 | 30.3 | |
| | Duration of study | 6 | ≤6 months | −0.31 | −0.66, 0.05 | 66.2 | |
| | | 3 | >6 months | −0.33 | −0.92, 0.25 | 50.8 | |
| | Type of intervention | – | ADCON-L gel | – | – | – | |
| | | 7 | Oxiplex gel | −0.33 | −0.65,−0.01 | 64.9 | |
| | | 2 | Other | −0.24 | −1.15, 0.68 | 58.1 | |
| BP | Name of outcomes | 2 | LSOQ score | −0.18 | −0.61, 0.25 | 70.5 | 40.2 |
| | | 4 | VAS score | 0.07 | −0.10, 0.24 | 0.0 | |
| | Duration of study | 4 | ≤6 months | −0.05 | −0.28, 0.19 | 56.0 | |
| | | 2 | >6 months | 0.03 | −0.50, 0.57 | 35.1 | |
| | Type of intervention | 1 | ADCON-L gel | 0.09 | −0.12, 0.30 | – | |
| | | 4 | Oxiplex gel | −0.13 | −0.36, 0.11 | 35.4 | |
| | | 1 | Other | 0.40 | −0.37, 1.17 | – | |
| ODI | Duration of study | 3 | ≤6 months | −0.04 | −0.22, 0.14 | 0.0 | |
| | | 3 | >6 months | −0.42 | −0.79, −0.04 | 0.0 | |
| | Type of intervention | 1 | ADCON-L gel | −0.02 | −0.23, 0.19 | – | |
| | | 4 | Oxiplex gel | −0.22 | −0.50, 0.05 | 0.0 | |
| | | 1 | Other | −0.48 | −1.25, 0.29 | – | |
| RP | Name of outcomes | 2 | LSOQ score | 0.28 | −0.47, 1.04 | 39.6 | 13.9 |
| | | 3 | VAS score | 0.09 | −0.17, 0.34 | 9.4 | |
| | Duration of study | 2 | ≤6 months | 0.20 | −0.36, 0.77 | 61.1 | |
| | | 3 | >6 months | 0.29 | −0.19, 0.77 | 0.0 | |
| | Type of intervention | 2 | ADCON-L gel | 0.08 | −0.27, 0.42 | 23.0 | |
| | | 2 | Oxiplex gel | 0.28 | −0.47, 1.04 | 39.6 | |
| | | 1 | Other | 0.43 | −0.36, 1.22 | – | |

LP: Leg pain; BP: Back pain; ODI: Oswestry disability index; RP: Radicular pain.

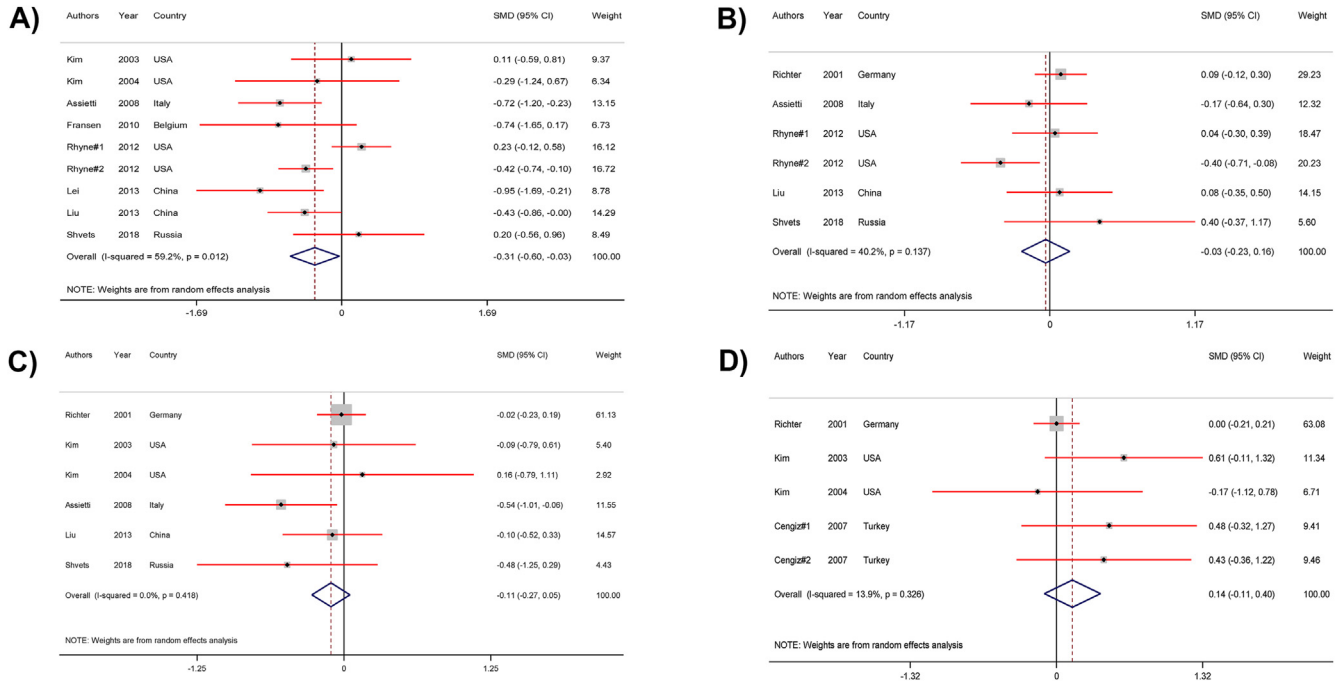


**Figure 2.** Meta-analysis standardized mean differences for A) leg pain, B) back pain, C) oswestry disability index, and D) radicular score in intervention with adhesion barrier gel and control groups (CI = 95%).

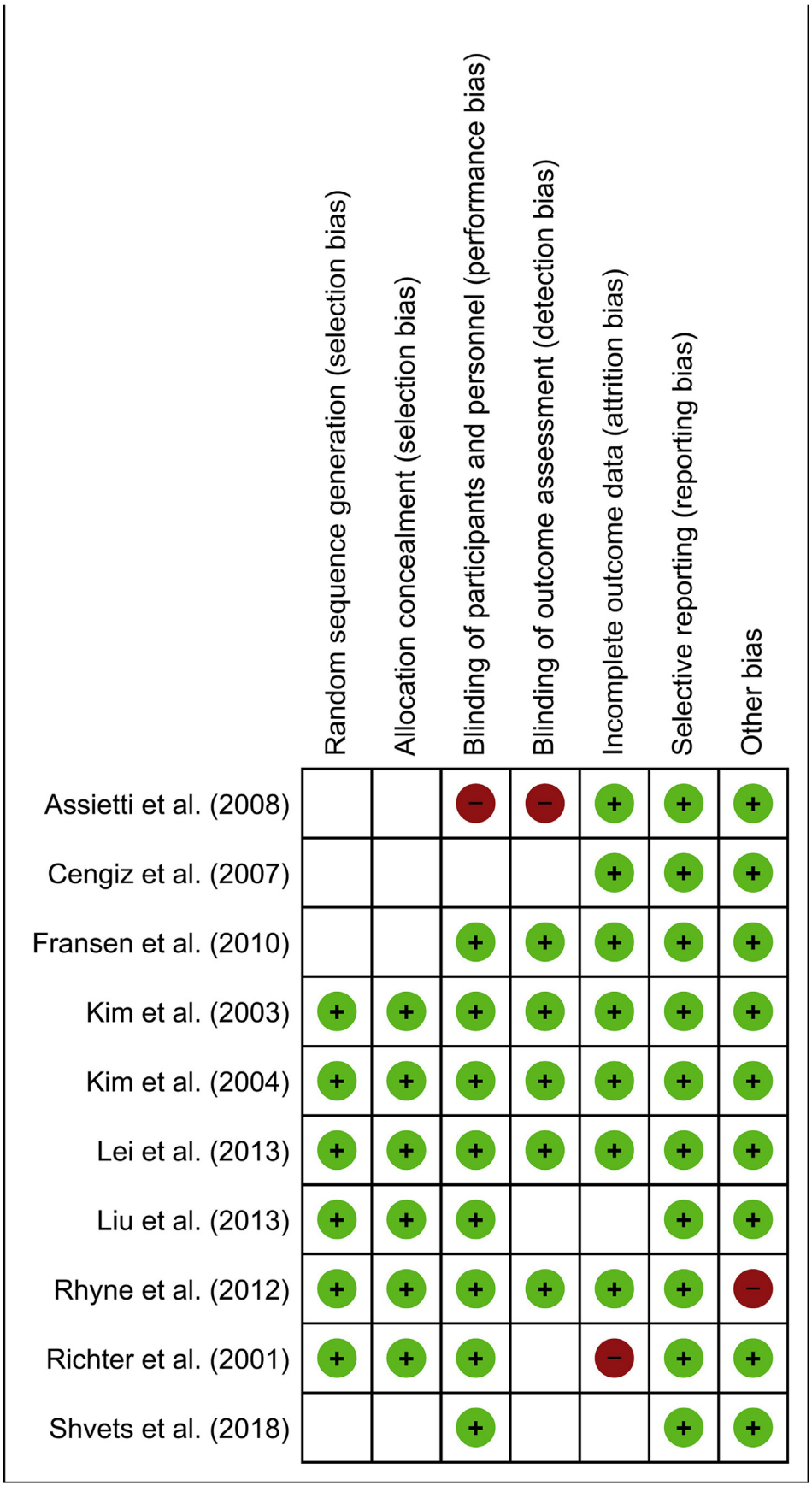


**Figure 3.** The methodological quality of included studies (risk of bias).

performed using the Cochrane Collaboration risk of bias tool has been presented in Figure 3.

## 4. Discussion

This is the first systematic review and meta-analysis which addressed the effects of the anti-adhesive barrier gels on functional outcome of the patients with single level lumbar disc surgery and laminectomy. Actually, we demonstrated that application of anti-adhesive barrier gels in lumbar disc surgery and laminectomy is associated with decreased leg pain and radiculopathy. However, the disability measured by the Oswestry disability index, low back pain and the gait was not affected significantly by application of the anti-adhesive barrier gels. These results indicate that the radicular pain and the leg pain could be reduced significantly by intraoperative application of the anti-adhesive barriers.

The rate of postoperative FBSS in those undergoing lumbar laminectomy is approximately 8–40% and this leads to re-operation and adhesion release in about 4–9% of the patients [12, 13]. The main cause of the FBSS is considered to adhesion formation between the paravertebral muscles and the dura matter which extends into the intervertebral foramina and leads to neural compression and clinical symptoms of LBP and radiculopathy [19]. The stages of adhesion formation could be classified as local inflammatory response (3–5 days after surgery), fibroblast proliferation and collagen deposition (2–3 weeks after surgery), and reconstruction and remodeling of the fibrillary connective tissue (months to years) [30, 31]. Postoperative hemorrhage and blood deposition on the dura is also among important factors of postoperative adhesions for which a hemovac is usually inserted and kept for 24-hour [19]. FBSS is multifactorial and thus the treatment should be based on the pathophysiology. Residual stenosis, dural tear, nerve damage (preoperative or intraoperative), incomplete recovery, poor musculature, excessive weight or post laminectomy instability are among the other factors that might affect the rate of FBSS and reduce the functional outcome [11]. Several methods have been proposed for prevention of epidural adhesions in patients undergoing lumbar laminectomy, which are based on providing a kind of barrier between the paravertebral muscles and the dura matter using biomaterials. The adhesion barrier gels are composed of biomaterials with large molecular weight, extensive biological function and complexity in structure [32]. These biomaterials have been tested in animal studies with promising results [19]. However, their clinical value in standard randomized clinical trials (RTCs) have been tested in limited studies with controversial results [17, 18, 21, 22, 23, 25, 26, 27, 28, 29]. We demonstrated that these adhesion barrier gels decreased the LP significantly while they do not affect the LBP and disability in short term (<6 months). In long-term follow-up (>6months) the adhesion barrier gel application is associated with decreased leg pain and the LBP. Based on the results of the current study we could recommend the application of adhesion barrier gels in patients undergoing single-level lumbar laminectomy for treatment if IVD disc herniation.

The included studies [17, 18, 21, 22, 23, 25, 26, 27, 28, 29] used various adhesion barrier gels with the approximately similar gradients and formula. ADCON-L (proteoglycan + porcine gel), Oxiplex®/Medishield (Carboxymethyl cellulose + polyethylene oxide) and Duraseal (Polyethyle glycol based) are the mostly used and available absorbable anti-adhesive barrier gels being applied in spinal surgery field. The ADCON-L is a bioabsorbable synthetic carbohydrate polymer gel being consisted of polyglycan ester and porcine-derived gelatin in phosphate-buffered saline [33]. The use of ADCON-L gel for prevention of adhesion has been widely used in various parts of the human and animal bodies including the intra-abdominal adhesions and orthopedic adhesions [20]. However, its application for prevention of epidural adhesions has been introduced in recent decade and the limited standard studies have addressed its effects in human individuals. The complications associated with application of ADCON-L gels are limited and not clinically significantly. Inhibition of spinal fusion, allergic reactions and muscle healing prevention have been reported [34]. The differences between the nature and gradients of these anti-adhesive barrier gels result in different complications and adverse events. However, none of the included studies [17, 18, 21, 22, 23, 25, 26, 27, 28, 29] reported any adverse events either in early or late phases. We also did not report any adverse events in the current meta-analysis as none was reported by any of the studies.

In conclusion, application of adhesion barrier gel in single level lumbar disc surgery is associated with deceased leg pain. However, its application does not affect the low back pain, disability and gait. Based on the results of the current meta-analysis of randomized clinical trial, application of the adhesion barrier gels in those undergoing lumbar laminectomy for treatment of IVD diseases is recommended which will improve the functional outcome both in short- and long-term. However, larger multicenter RCTs are required to empower the application of adhesion barrier gels in spine surgery.

## Declarations

### *Author contribution statement*

All authors listed have significantly contributed to the development and the writing of this article.

### *Funding statement*

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### *Data availability statement*

Data will be made available on request.

### *Declaration of interests statement*

The authors declare no conflict of interest.

### *Additional information*

No additional information is available for this paper.

## Acknowledgements

We would like to acknowledge the editorial assistance of Diba Negar Research Institute for improving the style and English of the manuscript.

## References

[1] M. Saxen, R.W. Rosenquist, The epidemiology and economic impact of spine pain, in: J. Mao (Ed.), Spine Pain Care: A Comprehensive Clinical Guide, Springer International Publishing, Cham, 2020, pp. 7–11.
[2] D. Hoy, C. Bain, G. Williams, L. March, P. Brooks, F. Blyth, et al., A systematic review of the global prevalence of low back pain, Arthritis Rheum. 64 (6) (2012) 2028–2037.
[3] N. Fouquet, A. Descatha, C. Ha, A. Petit, Y. Roquelaure, An epidemiological surveillance network of lumbar disc surgery to help prevention of and compensation for low back pain, Eur. J. Publ. Health 26 (4) (2016) 543–548.
[4] G.D. Schroeder, C.A. Guyre, A.R. Vaccaro, The epidemiology and pathophysiology of lumbar disc herniations, Semin. Spine Surg. 28 (1) (2016) 2–7.
[5] D.S. Kreiner, P. Matz, C.M. Bono, C.H. Cho, J.E. Easa, G. Ghiselli, et al., Guideline summary review: an evidence-based clinical guideline for the diagnosis and treatment of low back pain, Spine J. (2020).
[6] M.R. Farrokhi, M.H. Karimi, F. Ghaffarpasand, M. Sherafatian, MicroRNA-199a upregulation mediates lumbar intervertebral disc degeneration and is associated with clinical grades of degeneration, Turk. Neurosurg. 30 (1) (2020) 104–111.
[7] M. Sherafatian, H.R. Abdollahpour, F. Ghaffarpasand, S. Yaghmaei, M. Azadegan, M. Heidari, MicroRNA expression profiles, target genes, and pathways in intervertebral disk degeneration: a meta-analysis of 3 microarray studies, World Neurosurg. 126 (2019) 389–397.
[8] P. Kjaer, L. Korsholm, C. Leboeuf-Yde, L. Hestbaek, T. Bendix, Individual courses of low back pain in adult Danes: a cohort study with 4-year and 8-year follow-up, BMC Muscoskel. Disord. 18 (1) (2017) 28.

[9] C.S. Bailey, P. Rasoulinejad, D. Taylor, K. Sequeira, T. Miller, J. Watson, et al., Surgery versus conservative care for persistent sciatica lasting 4 to 12 months, N. Engl. J. Med. 382 (12) (2020) 1093–1102.
[10] C. Clancy, A. Quinn, F. Wilson, The aetiologies of failed back surgery Syndrome: a systematic review, J. Back Musculoskelet. Rehabil. 30 (3) (2017) 395–402.
[11] M.-Y. Liang, P.S. Pagel, Failed back surgery Syndrome, in: A. Abd-Elsayed (Ed.), Pain: A Review Guide, Springer International Publishing, Cham, 2019, pp. 655–657.
[12] E.H. Shin, K.J. Cho, Y.T. Kim, M.H. Park, Risk factors for recurrent lumbar disc herniation after discectomy, Int. Orthop. 43 (4) (2019) 963–967.
[13] S. Yin, H. Du, W. Yang, C. Duan, C. Feng, H. Tao, Prevalence of recurrent herniation following percutaneous endoscopic lumbar discectomy: a meta-analysis, Pain Physician 21 (4) (2018) 337–350.
[14] M.A. Alvi, P. Kerezoudis, W. Wahood, A. Goyal, M. Bydon, Operative approaches for lumbar disc herniation: a systematic review and multiple treatment meta-analysis of conventional and minimally invasive surgeries, World Neurosurg. 114 (2018) 391–407.e2.
[15] K. Amirdelfan, L. Webster, L. Poree, V. Sukul, P. McRoberts, Treatment options for failed back surgery Syndrome patients with refractory chronic pain: an evidence based approach, Spine (Phila Pa 1976) 42 (Suppl 14) (2017) S41–s52.
[16] M.R. Farrokhi, M. Lotfi, M.S. Masoudi, M. Gholami, Effects of methylene blue on postoperative low-back pain and functional outcomes after lumbar open discectomy: a triple-blind, randomized placebo-controlled trial, J. Neurosurg. Spine 24 (1) (2016) 7–15.
[17] S.L. Cengiz, A. Baysefer, Efficacy of Adcon-L gel or Healon-GV in epidural fibrosis after lumbar microdiscectomy, Neurosciences 12 (2) (2007) 109–113.
[18] V.V. Shvets, S.V. Kolesov, I.N. Karpov, A.A. Panteleyev, I.V. Scorina, DSJXп Gorbatyuk, Adhesion barrier gel Antiadgezin for degenerative lumbar spine disease 15 (2) (2018) (eng).
[19] R.S. Vediappan, A. Mascarenhas, A. Nguyen-Hoang, S. Anne Fong, A. Jukes, K. Richter, et al., Prevention of peridural adhesions in spinal surgery: assessing safety and efficacy of Chitogel with Deferiprone in a sheep model, J. Clin. Neurosci. 72 (2020) 378–385.
[20] H. Wang, W. Sun, D. Fu, Y. Shen, Y.Y. Chen, L.L. Wang, Update on biomaterials for prevention of epidural adhesion after lumbar laminectomy, J. Orthop. Translat. 13 (2018) 41–49.
[21] K.D. Kim, J.C. Wang, D.P. Robertson, D.S. Brodke, M. BenDebba, K.M. Block, et al., Reduction of leg pain and lower-extremity weakness for 1 year with Oxiplex/SP gel following laminectomy, laminotomy, and discectomy, Neurosurg. Focus 17 (1) (2004) Ecp1.
[22] K.D. Kim, J.C. Wang, D.P. Robertson, D.S. Brodke, E.M. Olson, A.C. Duberg, et al., Reduction of radiculopathy and pain with Oxiplex/SP gel after laminectomy, laminotomy, and discectomy: a pilot clinical study, Spine (Phila Pa 1976) 28 (10) (2003) 1080–1087, discussion 7-8.
[23] H.P. Richter, E. Kast, R. Tomczak, W. Besenfelder, W. Gaus, Results of applying ADCON-L gel after lumbar discectomy: the German ADCON-L study, J. Neurosurg. 95 (2 Suppl) (2001) 179–189.
[24] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, P. Jüni, D. Moher, A.D. Oxman, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, BMJ 343 (2011) d5928.
[25] P. Fransen, Reduction of postoperative pain after lumbar microdiscectomy with DuraSeal Xact adhesion barrier and sealant system, Spine J. 10 (9) (2010) 751–761.
[26] W. Lei, R.J. Ehmsen, R.P. Chiacchierini, J.L. Krelle, G.S. diZerega, Reduction of leg pain by oxiplex gel after lumbar discectomy in patients with predominant leg pain and elevated levels of lower back pain: a prospective, randomized, blinded, multicenter clinical study, J. Spinal Disord. Tech. 28 (8) (2015) 301–307.
[27] Z.C. Liu, Y. Li, Y. Zang, G. Cui, H.X. Sang, Z.S. Ma, et al., Clinical assessment of a CMC/PEO gel to inhibit postoperative epidural adhesion formation after lumbar discectomy: a randomized, control study, Arch. Orthop. Trauma Surg. 133 (3) (2013) 295–301.
[28] A.L. Rhyne, S.L. Blumenthal, E.H. Frank, K.Y. Hsu, K.D. Kim, J.A. Youssef, et al., Oxiplex reduces leg pain, back pain, and associated symptoms after lumbar discectomy, Spine (Phila Pa 1976) 37 (8) (2012) 631–641.
[29] R. Assietti, A. Mora, M. Brayda-Bruno, Use of carboxymethylcellulose/polyethylene oxide gel in microdiscectomy with interlaminectomy: a case series comparison with long-term follow-up, Spine (Phila Pa 1976) 33 (16) (2008) 1762–1765.
[30] Y. Sun, L. Wang, S. Sun, B. Liu, N. Wu, X. Cao, The effect of 10-hydroxycamptothecine in preventing fibroblast proliferation and epidural scar adhesion after laminectomy in rats, Eur. J. Pharmacol. 593 (1-3) (2008) 44–48.
[31] J. Zhu, Y. Li, W. Shen, C. Qiao, F. Ambrosio, M. Lavasani, et al., Relationships between transforming growth factor-beta1, myostatin, and decorin: implications for skeletal muscle fibrosis, J. Biol. Chem. 282 (35) (2007) 25852–25863.
[32] C. Luan, Z. Yang, B. Chen, Signal improvement strategies for fluorescence detection of biomacromolecules, J. Fluoresc. 26 (3) (2016) 1131–1139.
[33] G.M. Ivanic, P.T. Pink, F. Schneider, M. Stuecker, N.C. Homann, K.W. Preidler, Prevention of epidural scarring after microdiscectomy: a randomized clinical trial comparing gel and expanded polytetrafluoroethylene membrane, Eur. Spine J. 15 (9) (2006) 1360–1366.
[34] S.B. Kim, Y.J. Lim, Delayed detected unexpected complication of ADCON-L® gel in lumbar surgery, J. Korean Neurosurg. Soc. 48 (3) (2010) 268–271.