



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



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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 lumbar 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

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intervertebral foramina 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 explains 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 (≤ 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

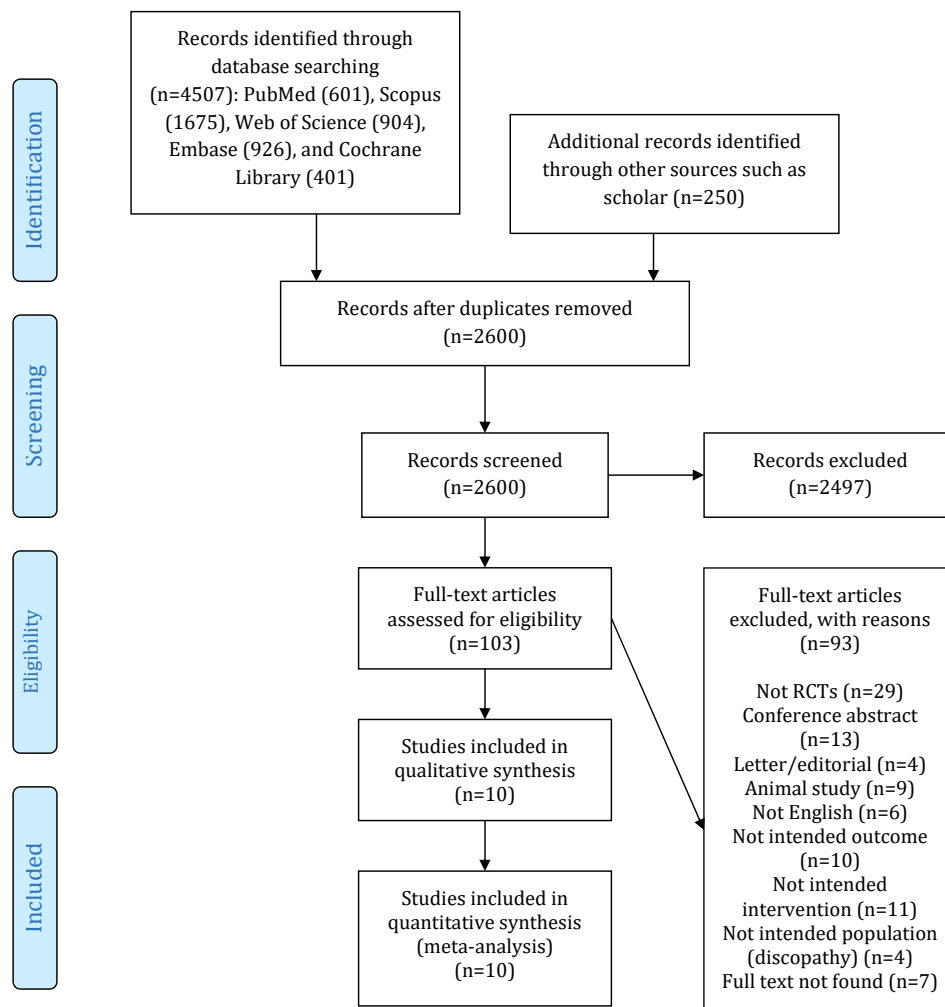


Figure 1. Literature search and review flowchart for selection of studies.

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 , I^2 : 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 , I^2 : 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.

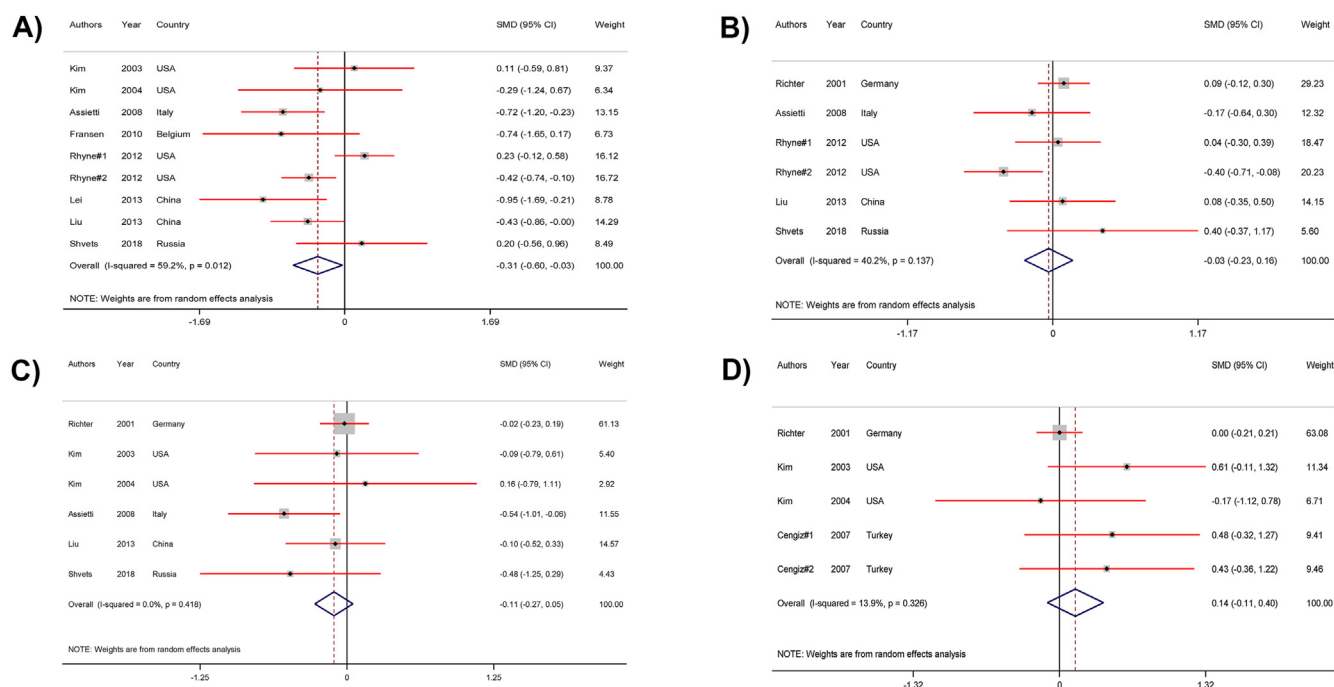
Authors (Ref)	Publication year	Sample size (control /intervention)	Country	Intervention (name and daily dose)	Schedule of supplementation intake (months)	Presented data	Age (y) (control, intervention)
Richter et al. [23]	2001	177/180	Germany	3–5 gr ADCON-L gel	6	BP, ODI, RP	42.9, 43.1
Kim et al. [22]	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 Antiadgezín 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
		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
		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
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
RP	Name of outcomes	2	LSOQ score	0.28	−0.47, 1.04	39.6
		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%).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Assietti et al. (2008)			—	—	+	+	+
Cengiz et al. (2007)					+	+	+
Fransen et al. (2010)			+	+	+	+	+
Kim et al. (2003)	+	+	+	+	+	+	+
Kim et al. (2004)	+	+	+	+	+	+	+
Lei et al. (2013)	+	+	+	+	+	+	+
Liu et al. (2013)	+	+	+			+	+
Rhyne et al. (2012)	+	+	+	+	+	+	—
Richter et al. (2001)	+	+	+		—	+	+
Shvets et al. (2018)			+			+	+

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 (pre-operative 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 (RCTs) 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 (>6 months) 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 (Polyethylene 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 decreased 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.

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

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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.

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