

Efficacy and Safety of Sodium Hyaluronate with 1,4-Butanediol Diglycidyl Ether Compared to Sodium Carboxymethylcellulose in Preventing Adhesion Formation after Lumbar Discectomy

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Objective: Epidural injection of hyaluronic acid may prevent adhesion formation after spine surgery, but the compounds used to stabilize hyaluronidase could interfere with its anti-adhesion effects. The present study was conducted as a clinical trial to evaluate the efficacy and safety of an experimental medical gel in preventing adhesion formation.

Methods: This study was designed as a multicenter, randomized, double-blind, and comparative controlled clinical trial with an observation period of 6 weeks. Subjects were randomly assigned into two groups: group A with sodium hyaluronate + 1,4-butanediol diglycidyl ether (BDDE) and group B with sodium hyaluronate + sodium carboxymethylcellulose (CMC). Visual analogue scale (VAS) of back and leg pain and the Oswestry disability index (ODI) and scar score ratings were assessed after surgery.

Results: Mean scar grade was 2.37±1.13 in group A and 2.75±0.97 in group B, a statistically significant difference (p=0.012). VAS of back and leg pain and ODI scores decreased significantly from baseline to 3 and 6 weeks postoperatively in both groups (p<0.001). However, VAS and ODI scores were not statistically different between groups A and B at baseline or at 3 and 6 weeks after operation (p>0.3). The number of adverse reactions related to the anti-adhesion gels was not statistically different (p=0.569), but subsequent analysis of nervous adverse reactions showed group B was superior with a statistically difference (p=0.027).

Conclusion: Sodium hyaluronate with BDDE demonstrated similar anti-adhesion properties to sodium hyaluronate with CMC. But, care should be used to nervous adverse reactions by using sodium hyaluronate with BDDE.

Key Words: Anti-adhesion · Scar formation · Lumbar discectomy · Sodium hyaluronate · 1,4-butanediol diglycidyl ether (BDDE) · Sodium carboxymethylcellulose (CMC)

INTRODUCTION

Failed back surgery syndrome (FBSS) is defined as the presence of persistent or severe disabling pain that continues after spinal surgery^{2,23,25}. According to previous studies, surgical

treatment of intervertebral disc herniation showed relatively good results in 90% of patients, but failed in 10%^{17,26}. Epidural fibrosis, which can be occurred in the course of surgical treatment, may be the cause of such poor results⁵, and in previous studies, was observed in 24% of recently failed lumbar spine surgeries^{19,32}. Moreover, the degree of back pain or nerve root pain could be reflective of the extent of spinal epidural

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†This study has not been presented in part elsewhere.

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fibrosis^{21,27}). Recently, various surgical materials prepared via polymer synthesis from natural resources to prevent or reduce adhesions after surgery have been developed^{12,18,28,31,32}). One such substance, hyaluronidase, has been administered to reduce swelling and edema in tissues by dissolving the glucosaminic bonds between hyaluronic acid and connective tissue. Utilizing this process, epidural injection of hyaluronic acid may prevent adhesion formation. However, the compounds used to stabilize hyaluronidase could interfere with its anti-adhesion effects. Previously, unpublished data from an effect test report of sodium hyaluronate + 1,4-butanediol diglycidyl ether (BDDE) demonstrated a greater anti-adhesion effect for BDDE than for other compounds of sodium hyaluronate. Here the authors conducted a clinical trial of an experimental medical gel composed of hyaluronate + BDDE to evaluate its effectiveness and safety in preventing adhesion formation.

MATERIALS AND METHODS

This clinical trial was designed as a multicenter, randomized, double-blind, and comparative controlled clinical trial. All subjects were volunteers and provided signed informed consent. In total, 74 cases that satisfied the selection criteria were enrolled for the study period of 24 months, and 68 cases were included in the final analyses, as 6 cases dropped out during the observation period (6 weeks for each case). The subjects were randomly divided into one of two groups according to type of anti-adhesion agent to be applied: group A received the anti-adhesion gel HyFence LV[®] (sodium hyaluronate + 1,4-Butanediol diglycidyl ether (BDDE), Cha Bio & Diostech, Seoul, Republic of Korea) and group B was treated with Guardix-SOL[®] (sodium hyaluronate + sodium carboxymethylcellulose, Genewel Co, Seongnam, Republic of Korea). All subjects received a randomly assigned anti-adhesion gel before wound closure after standard discectomy. Clinical outcomes were evaluated according to visual analogue scale (VAS) assessment and the Korean version of the Oswestry Disability Index (ODI) before surgery as well as 3 and 6 weeks after the investigational medical agents had been applied. Radiological outcomes were evaluated by magnetic resonance imaging (MRI), which was performed at 6 weeks after surgery, and graded according to scar formation by three different independent evaluators blinded to information about the subjects. Scar score ratings were graded according to the degree of dural scar score in the spinal canal as presented in Fig. 1 and Table 1. For each subject, five cross-sectional MR images were checked, and each cross-sectional image was divided into four quadrants, so that a total of 20 quadrant cross-sectional MR images per subject were evaluated²⁷). The checked scar grades of 3

different observers were all categorized by the scar grades and the mean scar grade was calculated.

The inclusion criteria for this study consisted of (1) patients older than 20 years and younger than 65 years of age; (2) diagnosis of lumbar disc herniation at spinal level L4-L5 or L5-S1 with radiculopathic symptoms refractory to conservative treatment for a minimum of 2 weeks; (3) scheduled for first surgery to remove single level and unilateral lumbar disc herniation; (4) could understand and follow instructions; and (5) could provide written consent to participate in the clinical trial. The exclusion criteria consisted of (1) patients with multi-level, far lateral or bilateral lumbar disc herniation; (2) those with degenerative spinal cord disease or scoliosis; (3) exhibited hyaluronic acid-sensitive side effects; (4) involved lymphatic or blood clotting disorders or were administered a blood coagulant; (5) had uncontrolled diabetes; (6) received oral steroid medication within 4 weeks, epidural steroid injection within 10 days or were administered aspirin and/or non-steroidal anti-inflammatory agents within 7 days from the baseline study period; (7) had collagen-vascular disease, self-immune diseases such as rheumatoid arthritis or systemic lupus erythematosus, or malignant tumors within 5 years; (8) demonstrated spinal cord angiography or lumbar puncture within 24 hours from the baseline study period; (9) showed reduced immunity or abnormal labo-

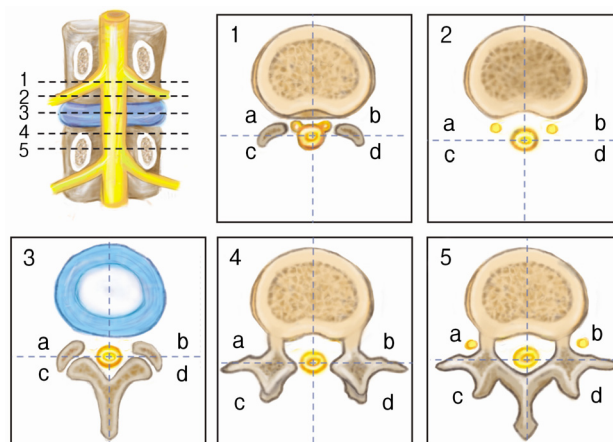


Fig. 1. The positions of five standard cross-sectional magnetic resonance images.

Table 1. Peridural scar score

Scar score	Description
0	No/trace scar
1	0-25% of quadrant filled with scar
2	25-50% of quadrant filled with scar
3	50-75% of quadrant filled with scar
4	>75% of quadrant filled with scar

ratory tests (hematologic, blood chemical, and urine test) during screening tests; (10) have had or currently had serious disability affecting the cardiovascular, digestive, respiratory, endocrine, or central nervous system, or clinical mental illness; (11) participated in other clinical trials within 30 days; or (12) were pregnant, lactating, or on contraceptive medication.

Student's t-test and ANOVA test were conducted to estimate the reliability of radiological and clinical outcomes for each group. Kruskal-Wallis test was used to compare outcomes before application and at follow-up. The mean scar grade of each group was considered as interval scales for easier comparison between the groups, although this should be considered as ordinal scales. All statistical analyses were performed using SPSS software version 12 (SPSS Inc., Chicago, IL, USA), and statistical significance was defined as $p < 0.05$.

RESULTS

The results concerning scar formation are presented in Table 1. No statistical difference was observed in the demographic data between groups A and B. Scar scores differed according to the different anti-adhesion gels applied, and comprised 3 cases of grade 0, 21 cases of grade 1, 35 cases of grade 2, 21 cases of grade 3, and 22 cases of grade 4 scarring in group A. Group B comprised no cases of grade 0, 9 cases of grade 1, 37 cases of grade 2, 27 cases of grade 3, and 29 cases of grade 4 scarring. Statistical analysis using the chisquare test generated a result of 0.048. The mean scar grade for each group was 2.37 ± 1.13 in group A and 2.75 ± 0.97 in group B, which was a statistically significant difference ($p = 0.012$) (Table 2).

In group A, mean back pain VAS decreased significantly ($p < 0.001$) from a baseline of 51.94 ± 48.72 to a 3-week postoperative score of 20.28 ± 20.57 and a 6-week postoperative score of 21.35 ± 22.77 . Similarly, in group B, preoperative

mean back pain VAS score decreased significantly ($p < 0.001$) from 48.72 ± 27.87 to 25.24 ± 24.45 at 3 weeks postoperative and 20.41 ± 21.97 at 6 weeks postoperative. Mean leg pain VAS significantly decreased ($p < 0.001$) from a baseline of 63.47 ± 22.79 to a 3-week postoperative score of 23.22 ± 23.75 and 6-week postoperative score of 20.59 ± 26.05 in group A, and similarly, from a preoperative score of 66.59 ± 20.11 to a 3-week postoperative score of 28.76 ± 27.30 and a 6-week postoperative score of 23.32 ± 26.92 in group B ($p < 0.001$). Similar to the VAS results, in group A, mean ODI score decreased significantly ($p < 0.001$) from a baseline score of $42.11 \pm 16.89\%$ to $27.93 \pm 14.92\%$ at 3 weeks postoperative and $22.64 \pm 14.87\%$ at 6 weeks postoperative. In group B, mean preoperative ODI score decreased from $44.72 \pm 19.11\%$ to $31.26 \pm 15.41\%$ at 3 weeks postoperative and $26.62 \pm 16.98\%$ at 6 weeks postoperative (Fig. 2). Altogether, back pain VAS, leg pain VAS and ODI scores were not statistically different between the two groups at baseline or at 3 and 6 weeks after operation ($p > 0.3$).

Observed adverse reactions are summarized in Table 3. Adverse reactions were categorized as musculoskeletal and connective tissue disorders; injury, poisoning and procedural complications; gastrointestinal disorders; nervous system disorders; general disorders and administration site conditions; renal and urinary disorders; infections and infestations; investigations; psychiatric disorders; skin and subcutaneous tissue disorders; respiratory, thoracic and mediastinal disorders; metabolism and nutrition disorders; hepatobiliary disorders; or vascular disorders. Relevant disease or symptoms for each category are listed in Table 3. In group A, 113 events of an adverse reaction among 33 cases (91.7%) were recorded, while 98 events among 24 cases (68.6%) were observed in group B. Although the number of cases of an adverse reaction between the two groups was statistically different ($p = 0.018$), the number of adverse reactions was not statistically different ($p = 0.569$). Most of the adverse reactions were minor (two major adverse reactions in group B included one case of wound infection and a case of intervertebral disc protrusion), and all adverse reactions were unrelated to the device. In regards to adverse reaction category, nervous system disorders were more frequently recorded for group A than group B; 14 events were recorded among 12 patients in group A, while 7 events among 4 patients were noted in group B ($p = 0.027$). But nervous adverse reactions broadly included symptoms of paraesthesia, dizziness, hypoesthesia, carpal tunnel syndrome, cerebral arteriosclerosis, cervicobrachial syndrome, headache and radicular pain. Concerning the presenting symptoms of the adverse nervous system disorders, five events of paraesthesia in group A and one event in group B were observed; one event of dizziness in group A and 4 events in group B were recorded; 4 events

Table 2. Scar scores between the two groups

	Group A	Group B	p-value
Device	HyFence LV	Guardix-SOL	
Composition	HA+CMC	HA+BDDE	
N	34	34	
Grade 0	3	0	0.048
Grade 1	21	9	
Grade 2	35	37	
Grade 3	21	27	
Grade 4	22	29	
Mean Grade	2.37 ± 1.13	2.75 ± 0.97	0.012

HA, sodium hyaluronate; CMC, sodium carboxymethylcellulose; BDDE, 1,4-Butanediol diglycidyl ether

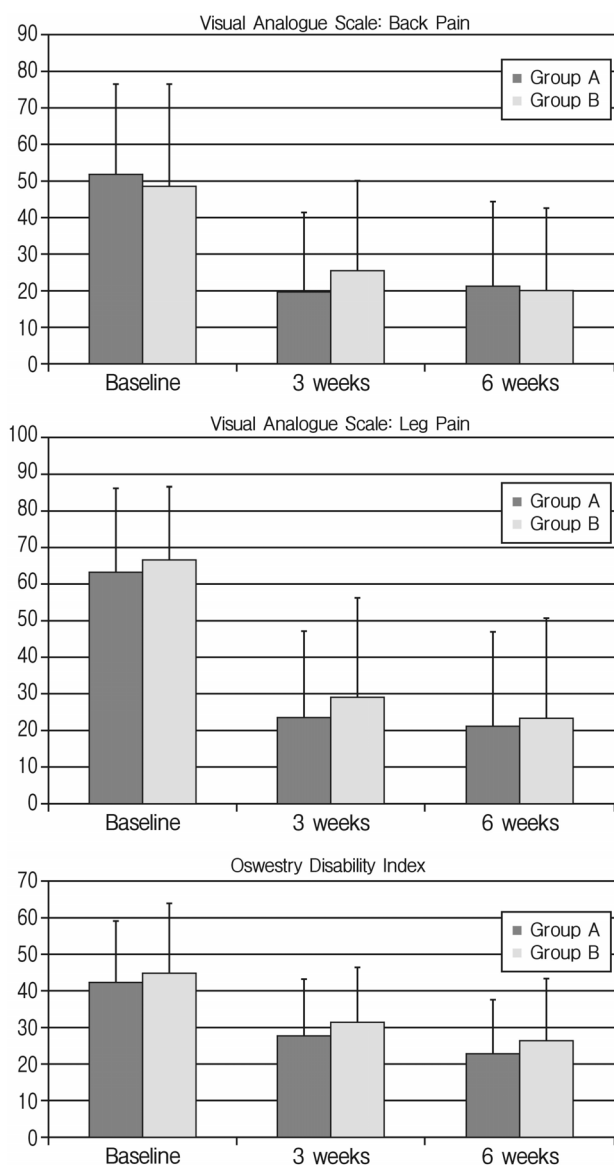


Fig. 2. Clinical results between the two groups: visual analog scale for back and leg pain, and Oswestry disability index.

of hypoesthesia in group A and one event in group B were noted; one event each of carpal tunnel syndrome, cerebral arteriosclerosis, cervicobrachial syndrome and radicular pain were recorded in group A; and finally, a single event of headache was reported in group B. Subsequent analysis of nervous adverse reactions that could related to the anti-adhesion gels (e.g. paraesthesia, hypoesthesia and radicular pain) showed a statistically difference ($p=0.013$). In other adverse reaction categories, no statistical difference was observed.

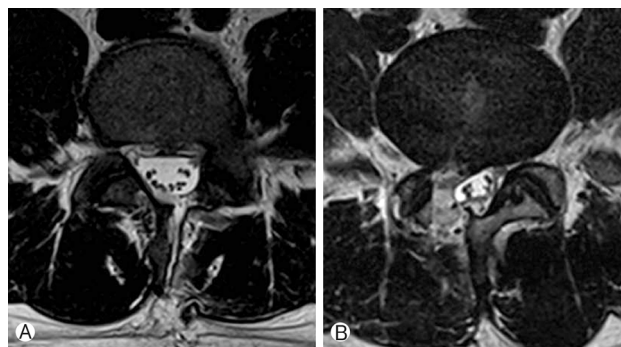


Fig. 3. Postoperative MR. (A) Scantly observed scar tissue; and (B) Compressive scar tissue in post-laminectomy site.

DISCUSSION

Postoperative fibrosis is a natural course of wound healing^{12,24}. Fibroblasts, originating from the overlying muscles and following extension of postoperative hematoma into the vertebral canal, release excessive extracellular matrix and cause the abundance and strong adhesion of the tissue^{16,29}. Thus, the migration of fibroblasts from the raw surface of the erector spine musculature was stated as the source of postoperative scar tissue^{10,16}. But, epidural adhesion was considered as a major contributing factor to postsurgery radicular pain and lower extremity weakness after laminectomy^{3,7,11,18,19,22,24,27}. Moreover, epidural adhesion is thought to be with the increased complication rates associated with spinal reinterventions^{4,6,9,13}. A general feature seems to be the requirement for direct contact between exposed dura and invading fibroblasts, thereby allowing for the generation of localized dense fibrotic tissue and tethering of the thecal sac and nerve roots²⁴. Numerous experimental and clinical studies had focused to prevent epidural adhesion formation using prophylactic intervention. Such treatments have included modified surgical approaches, antiinflammatory agents, antibiotics, and a wide variety of biological and synthetic barriers, including fat grafts, hyaluronan, collagen, gelatin foam, polylactide films, ADCON-L and more recently, Oxiplex1/SP Gel.^{1,6,8,11,13-15,20,21,24,27,33} In general concept, the ideal agent for preventing peridural adhesion and fibrosis should include the following properties: (1) prevention of scar tissue adhesion to the dural tissues, (2) prevention of the development of leptomeningeal arachnoiditis, (3) no potential to impair dural healing following tearing and CSF leakage and (4) no capability to induce excessive inflammation around neural tissues²⁴.

In the present study, scar scores were significantly different between the two medical agents. The mean scar grade for group A was 2.46 ± 0.71 and 2.70 ± 0.71 for group B, a statistically

Table 3. Adverse effects observed between the two groups

	Group A (n=36)	Group B (n=35)	p-value
Cases of adverse reactions	n=33 (91.7%)	n=24 (68.6%)	0.018
Events of adverse reactions	113	98	0.569
Major adverse reactions	0	2	
Minor adverse reactions	113	96	0.146
Device related adverse reactions	0	0	
Non-device related adverse reactions	113	98	N/A
Adverse Reactions			
Musculoskeletal and connective tissue disorders ¹	23 (n=12, 33.3%)	18 (n=9, 25.7%)	0.482
Injury, poisoning and procedural complications ²	21 (n=16, 44.4%)	18 (n=12, 34.3%)	0.381
Gastrointestinal disorders ³	20 (n=16, 44.4%)	18 (n=12, 34.3%)	0.381
Nervous system disorders ⁴	14 (n=12, 33.3%)	7 (n=4, 11.4%)	0.027
General disorders and administration site conditions ⁵	8 (n=8, 22.2%)	9 (n=8, 22.9%)	0.949
Renal and urinary disorders ⁶	7 (n=7, 19.4%)	7 (n=7, 20.0%)	0.953
Infections and infestations ⁷	5 (n=3, 8.3%)	6 (n=6, 17.1%)	0.265
Investigations ⁸	5 (n=4, 11.1%)	4 (n=4, 11.4%)	0.966
Psychiatric disorders ⁹	4 (n=4, 11.1%)	2 (n=2, 5.7%)	0.413
Skin and subcutaneous tissue disorders ¹⁰	3 (n=2, 5.6%)	3 (n=3, 8.6%)	0.620
Respiratory, thoracic and mediastinal disorders ¹¹	2 (n=2, 5.6%)	2 (n=1, 2.9%)	0.572
Metabolism and nutrition disorders ¹²	0 (n=0, 0.0%)	2 (n=2, 5.7%)	0.146
Hepatobiliary disorders ¹³	0 (n=0, 0.0%)	2 (n=1, 2.9%)	0.307
Vascular disorders ¹⁴	1 (n=1, 2.8%)	0 (n=0, 0.0%)	0.321

¹Back pain, pain in an extremity, musculoskeletal pain, intervertebral disc protrusion, muscular weakness, arthralgia, musculoskeletal stiffness, myalgia, and myofascial pain syndrome; ²Procedural pain, post procedural complication, procedural hypertension, wound secretion, contusion, open wound, post procedural constipation, post procedural discharge, post procedural discomfort, post procedural edema, post procedural swelling, procedural nausea, and toxicity to various agents; ³Constipation, nausea, dyspepsia, vomiting, aphthous stomatitis, diarrhea, gastrointestinal disorder, abdominal distension, abdominal pain, dry mouth, hematochezia, and reflux esophagitis; ⁴Paraesthesia, dizziness, hypoesthesia, carpal tunnel syndrome, cerebral arteriosclerosis, cervicobrachial syndrome, headache, and radicular pain; ⁵Pyrexia, chills, hernia, pain, and tenderness; ⁶Dysuria and urinary retention; ⁷Nasopharyngitis, gastroenteritis, upper respiratory tract infection, and wound infection; ⁸Increased blood pressure, increased alanine aminotransferase, and increased aspartate aminotransferase; ⁹Insomnia, anxiety, and depression; ¹⁰Urticaria, dermatitis contact, pruritus, and rash; ¹¹Atelectasis, cough, dyspnea, and oropharyngeal pain; ¹²Decreased appetite and hypoalbuminemia; ¹³Hepatic cyst and hepatic steatosis; ¹⁴Hypertension

significant difference ($p=0.05$). Moreover, all back pain VAS, leg pain VAS and ODI scores decreased significantly ($p<0.001$) from baseline to 3 and 6 weeks postoperative. These results indicated that 1,4-butanediol diglycidyl ether is a more effective compound than carboxymethyl cellulose in stabilizing sodium hyaluronate, and substantiated our results from a previous, unpublished preliminary study in rats. Although no absolute proof has been presented and the invasion was needed, the authors discerned that 1,4-butanediol diglycidyl ether is a more effective stabilizer of sodium hyaluronate after spine operation as a result of its molecular structure and other unknown variables. However, interestingly, although all of the adverse reactions observed in this study were not related to the agent, nervous system disorders were more frequently reported in 1,4-butanediol diglycidyl ether administered sub-

jects with statistical significance ($p=0.027$). Indeed, the presenting symptoms were directly correlated with nerve root irritation such as paraesthesia or hypoesthesia. Therefore, careful patient selection in the use of sodium hyaluronate with 1,4-butanediol diglycidyl ether is needed and more specific study concerning this issue is warranted.

There were some limitations of this study that warrant consideration. First, this study was initially designed as a noninferiority test of sodium hyaluronate with 1,4-butanediol diglycidyl ether compared the other anti-adhesive products; therefore, further compatible randomized control study is needed. Second, scar formation was checked not by clinical study, but by imaging studies. Therefore, the actual scar formation is not clear. Indeed, the postoperative peridural scar was commonly studied after postoperative 6 months, but this study was evalua-

ted at 6 weeks after operation. So, the MR finding is subjective postoperative epidural scar, but, it could be misjudge of the epidural soft tissue edema or hemorrhage. So, further elongated study is needed to confirm the scar formation by the adhesion formation materials. Despite these limitations, the present study was designed as a multicenter, randomized, single-blind, and comparative controlled clinical trial. The results indicated that stabilizing materials of sodium hyaluronate interfere with the anti-adhesive function thereof after spine surgery and that 1,4-butanediol diglycidyl ether is a more effective compound than carboxymethylcellulose in stabilizing sodium hyaluronate.

CONCLUSION

Sodium hyaluronate with 1,4-butanediol diglycidyl ether demonstrated better anti-adhesion properties than sodium hyaluronate with carboxymethylcellulose in patients after lumbar discectomy. However, further research could help to know its ambiguous effect on the neural tissues.

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