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Clinical assessment of a CMC/PEO gel to inhibit postoperative epidural adhesion formation after lumbar discectomy: a randomized, control study

Zhi-chen Liu · Yang Li · Yuan Zang · Geng Cui · Hong-xun Sang · Zhen-sheng Ma · Liang Kong · Wei Lei · Zi-xiang Wu

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Abstract
Purpose To evaluate effectiveness of carboxymethylcellulose/polyethylene oxide (CMC/PEO) gel in improving clinical outcomes after the first-time lumbar discectomy.
Method Ninety-three patients with herniated lumbar disc at L4–L5 or L5–S1 were enrolled and randomized into two groups: CMC/PEO gel treatment group and control group. All the patients underwent laminotomy and discectomy by posterior approach. The preoperative and postoperative Oswestry Disability Index (ODI) and Visual Analogue Scale (VAS) scores for lower-back pain and leg pain were analyzed and compared between two groups at 30- and 60-day time points.
Results No patient presented with any clinically measurable adverse event during surgery. There were no significant differences between the treated group and the control group on the preoperative ODI and VAS scores. In general, the ODI and VAS scores decreased in both groups at all the time points. At the 30-day time point, the VAS scores for back pain and leg pain and the ODI scores in treatment group were lower by 9.9 % ($P = 0.0302$), 27.0 % ($P = 0.0002$) and 16.3 % ($P = 0.0007$) than those in control group. And at the 60-day time point, the ODI and VAS scores further decreased in both groups. The VAS scores for leg pain in treatment group were lower by 4.5 % than that in the control group ($P = 0.0149$). However, no significant difference was detected between two groups on the ODI and VAS scores for back pain.
Conclusions The results demonstrated that CMC/PEO gel is effective in reducing posterior dural adhesions in the spine with no apparent safety issues. It can improve patients' postoperative clinical outcome.

Keywords Carboxymethylcellulose · Polyethylene oxide · Epidural · Fibrosis · Discectomy

Z. Liu · Y. Li · Y. Zang · H. Sang · Z. Ma · W. Lei (✉) · Z. Wu (✉)
Institute of Orthopaedics, Xijing Hospital, The Fourth Military Medical University, No. 17 Changlexi Road, Xi'an 710032, Shanxi, People's Republic of China
e-mail: leiwei@fmmu.edu.cn

Z. Wu
e-mail: wuzixiang@fmmu.edu.cn

Z. Liu
e-mail: jackltt218@126.com

Y. Li
e-mail: yanglee.112@163.com

Y. Zang
e-mail: yuanzang@fmmu.edu.cn

H. Sang
e-mail: sanghx@fmmu.edu.cn

Z. Ma
e-mail: mazhensheng@fmmu.edu.cn

G. Cui
Institute of Orthopaedics, the General Hospital of P.L.A., Beijing 100000, People's Republic of China
e-mail: gengcui@163.com

L. Kong
Department of Implantology, School of Stomatology, The Fourth Military Medical University, Changlexi Road No. 17, Xi'an 710072, People's Republic of China
e-mail: kongliang@fmmu.edu.cn

Introduction

The number of back surgeries performed to relieve lower-back pain in the United States rose from 300,413 in 1994 to 392,948 in 2000 [1]. Best estimates suggest that although 60 % or more of initial back surgeries have a successful outcome, many are not successful [2, 3]. In a retrospective study of 24,882 patients who underwent spinal surgery in Washington State from 1990–1993, 19 % required reoperation for pain or complications of surgery over the ensuing 11 years [4]. Patients who have chronic, disabling lower-back pain after one or more spinal surgeries are said to have failed back surgery syndrome [5]. Failed back surgery syndrome (FBSS) is a clinical syndrome in which patients have persistent back and/or leg pain after one or more surgical procedures aimed at correcting their lumbosacral disease [6, 7]. There are many reasons for failure of lumbar surgery. Among them, epidural fibrosis was considered to be closely related to FBSS [8, 9]. Postoperative epidural fibrosis is an unavoidable adverse effect of lumbar disc surgery because of the healing process [10, 11]. It is assumed that epidural fibrosis is responsible for as much as 25 % of all FBSS. Because no treatment has been shown to be consistently effective, prevention of scar formation has been a focus of surgical technique [12].

To prevent epidural fibrosis, many materials and methods have been studied including free or pedicle fat grafts [13, 14]; absorbable gelatin films and sponges, and cellulose mesh [14, 15]; hyaluronic acid [16, 17]; hydroxycamptothecin [6], and local or systemic pharmaceuticals, such as methylprednisolone and dexamethasone [18–22]. However, no golden-standard treatment has been established till now. Carboxymethylcellulose/polyethylene oxide (CMC/PEO) has been demonstrated safe and there were no adverse events in animal studies. This study aimed to explore and assess the safety and effectiveness of using CMC/PEO gel to decrease epidural fibrosis and improve clinical outcomes in lumbar spinal surgery. MediShield™ Gel is a flowable gel. The gel is a sterile, absorbable, combination of polyethylene oxide (PEO) and sodium carboxymethylcellulose (CMC). And Medtronic is the manufacturer of this gel (Medtronic, Inc. 710 Medtronic Parkway Minneapolis, MN 55432-5604, Minnesota, USA).

Patients and methods

This randomized, single-blind, multicenter, clinical trial evaluated the safety of CMC/PEO gel in reducing postoperative epidural fibrosis and related symptoms after surgery for herniated lumbar disc at L4–L5 or L5–S1. The clinical study proposal was approved by the medical ethical committee of The Fourth Military Medical University. From Oct. 2005 to Mar. 2010, 93 patients with unilateral lumbar intervertebral disc herniation at L4–L5 or L5–S1, associated with radiculopathy were enrolled and randomized into two groups: CMC/PEO gel treatment group and control group according to the table of random number (Table 1). They were selected from patients who presented at the Department of Orthopaedic, Xijing Hospital and Peking University Third Hospital. All patients were provided with the protocol and the informed consent document. All patients signed the document.

Demographic characteristics

Full analysis set (FAS) results show that the experimental group and control group, gender, age, height, weight, medical history and medical examination, the situation is more, by rank sum test showed no significant difference ($P > 0.05$) (Tables 2, 3).

Inclusion criteria

The patients were adults (ranged from 18 to 70 years) scheduled to undergo their first surgery for removal of a unilateral L4–L5 or L5–S1 disc herniation, associated with radiculopathy. Specific inclusion criteria required signs and symptoms of lumbar or lumbosacral radiculopathy affecting one predominant nerve root level, radiologic evidence of nerve root compression, and/or confirmed existence of an extruded or sequestered disc fragment at L4–L5 or L5–S1 compatible with clinical signs and symptoms. Preoperative laboratory test results needed to be within normal limits or deemed not to be of clinical significance by the investigator. The patients included in the study underwent at least 2 weeks of non-operative treatment without resolution of pain, which the surgeon could waive if the patient was experiencing intractable pain or progressive loss of neurologic function. During the 2-week non-operative period, the physician treated the patient as necessary with physical therapy, narcotics, or any other non-disqualifying treatments that would alleviate the patient's discomfort. No patient had epidural steroid treatment withheld to qualify for the study.

Exclusion criteria

Patients were excluded if they had undergone previous spinal surgery, had history of cancer within 5 years, had been treated with epidural steroids within 4 weeks or oral steroids within 10 days of the proposed surgery, and/or had received aspirin or other non-steroidal anti-inflammatory drugs within 7 days of the proposed surgery. Patients who had received myelograms or lumbar punctures within 24 h before surgery also were excluded. Patients were excluded

Table 1 Random number table of two groups

Group	Enroll	Not meeting inclusion criteria	Met exclusion criteria	Dropout	Eligible subject
Center 1					
CMC/PEO	31	2	2	0	27
Control	17	0	3	1	13
Total	48	2	5	1	40
Center 2					
CMC/PEO	29	2	0	0	27
Control	16	0	0	1	15
Total	45	2	0	1	42
Summary					
CMC/PEO	60	4	2	0	54
Control	33	0	3	2	28

Table 2 Gender composition analysis

	CMC/PEO	Control	Statistics (Z)	P value
Male	37 (63.79 %)	18 (62.07 %)	0.15	0.88
Female	21 (36.21 %)	11 (37.93 %)	0.15	0.88
Total	58	29	0.15	0.88

Table 3 Age, height and weight in the treatment and control group

	CMC/PEO ($N = 29$)	Control ($N = 15$)	Statistics (Z)	P value
Age	40.45 ± 13.92	36.67 ± 11.98	−0.83	0.4079
Height	168.90 ± 7.99	167.73 ± 6.73	0.06	0.9505
Weight	63.97 ± 9.25	62.10 ± 6.26	−0.20	0.8421

Z rank-sum test statistic and P value

Table 4 VAS scores for both lower-back pain and leg pain in the treatment and control group

	CMC/PEO ($N = 60$)	Control ($N = 33$)	Z scores	P value
Lower-back pain				
Baseline	4.62 ± 2.51	4.90 ± 2.06	0.41	0.6805
30 days	1.47 ± 1.83	2.13 ± 1.78	2.48	0.0132
60 days	0.78 ± 1.45	0.85 ± 0.81	1.65	0.0986
0–30 days	3.14 ± 3.09	2.77 ± 2.33	−0.84	0.3989
0–60 days	3.84 ± 2.89	4.05 ± 2.02	0.22	0.8249
Decrease	76.78 %	80.22 %	−1.25	0.21
Leg pain				
Baseline	6.35 ± 2.13	5.72 ± 2.22	−1.18	0.238
30 days	1.20 ± 1.62	2.30 ± 1.99	3.16	0.0016
60 days	0.46 ± 0.93	0.81 ± 0.84	2.35	0.0187
0–30 days	5.15 ± 2.40	3.42 ± 2.63	−2.87	0.0041
0–60 days	5.89 ± 2.25	4.92 ± 2.18	−2.06	0.0395
Decrease	90.74 %	86.22 %	−2.43	0.0149

if they had collagen vascular diseases, hemorrhagic diseases or autoimmune diseases. Patients were also excluded if they had severe lumbar scoliosis (>10°). Other exclusion criteria specified any concurrent disease that, in the surgeon's opinion, could influence the outcome of the proposed surgery, any postoperative involvement in a current or anticipated worker's compensation claim, or any involvement in current or anticipated personal injury litigation. Patients were excluded intraoperatively for dural entry, discovery of intraspinal tumor, the need to involve more than one level, exploration of the contralateral side, placement of an epidural fat pad, or retention of a hemostat.

Randomization

All patients randomized into two groups (test group: 60; control group: 33) according to the table of random number. Randomization was assigned when the patient's surgical procedure was completed to the point at which hemostasis was assured and the surgeon was ready to close the operative site. At that time, the sponsor was called for patient assignment: to receive CMC/PEO gel or not to receive any additional adhesion prevention treatment (control condition). Any hemostatic agent used during surgery was removed before closure of the surgical site. All the patients underwent closure in the surgeon's routine fashion. The test patients received sufficient CMC/PEO gel to coat the nerve roots and fill the operative site (~3 mL).

Surgical procedure

All the patients underwent laminotomy and discectomy by posterior approach. After nucleus pulposus were removed and hemostasis was completed, any hemostatic agents used during surgery were removed. Before the

Table 5 ODI scores for both lower-back pain and leg pain in the treatment and control group

	CMC/PEO ($N = 60$)	Control ($N = 33$)	Z scores	P value
FAS				
Baseline	26.29 ± 10.02	24.86 ± 8.11	−0.89	0.3746
30 days	8.03 ± 8.39	12.14 ± 7.56	3.07	0.0021
60 days	5.22 ± 6.82	4.86 ± 3.20	1.39	0.1644
0–30 days	18.26 ± 12.44	12.72 ± 7.60	−2.39	0.0167
0–60 days	21.07 ± 11.94	20.00 ± 8.12	−0.47	0.6394
Decrease	77.87 %	79.25 %	−1.72	0.0853
PPS				
Baseline	25.87 ± 10.22	24.61 ± 8.14	−0.75	0.451
30 days	7.65 ± 8.23	12.29 ± 7.66	3.31	0.0009
60 days	4.80 ± 6.41	4.75 ± 3.20	1.60	0.1087
0–30 days	18.22 ± 12.77	12.32 ± 7.42	−2.46	0.014
0–60 days	21.07 ± 12.26	19.86 ± 8.24	−0.48	0.6281
Decrease	78.63 %	79.41 %	−1.94	0.0527

FAS full analysis set, *PPS* per protocol set

surgeon was going to close the incision, patients received different treatments: CMC/PEO gel (treatment group) or not any additional adhesion prevention treatment (control group). The patients in treatment group received sufficient CMC/PEO gel to coat the nerve roots and fill the operative site. Then, all the patients underwent routine closure.

Outcomes assessment

Severity of lower-back pain and leg pain were assessed at 30- and 60-day intervals postoperation with the Visual Analogue Scale (VAS) pain scale (10 cm). Functional disability was assessed by Oswestry Disability Index (ODI). Neurological function recovery was also evaluated by physical examinations. They were compared to baseline within both groups and with each other at various time intervals.

Statistical analysis

Changes from baseline laboratory values were analyzed using the paired t test or the Wilcoxon matched-pairs signed-rank test. Analyses of variance (ANOVA) were used to evaluate changes from baseline and to compare the two groups (CMC/PEO gel and control groups). For all analyses, P values <0.05 were considered significant.

Results

All the patients (60 in the PEO/CMC group and 33 in the control group) tolerated the surgical procedures well and no patient presented with any clinically measurable adverse event during surgery at the time of the application of the gel (Tables 4, 5). There were no statistically significant differences between the treated group and the control group on

Table 6 Sixty days after surgery, the results of the deep tendon reflexes in different groups

	CMC/PEO	Control	Statistics (Z)	P value
Right knee tendon				
Exist	28 (96.55 %)	15 (100.00 %)	−0.67	0.5021
Weaken or disappear	1 (3.45 %)	0 (0.00 %)		
Total	29	15		
To normal rate (%)	3.45	0	0.67	0.5021
Left knee tendon				
Exist	27 (93.10 %)	13 (86.67 %)	0.67	0.5022
Weaken or disappear	2 (6.90 %)	2 (13.33 %)		
Total	29	15		
To normal rate (%)	6.9	13.33	−0.67	0.5022
Right Achilles tendon				
Exist	24 (82.76 %)	13 (86.67 %)	−0.31	0.7546
Weaken or disappear	5 (17.24 %)	2 (13.33 %)		
Total	29	15		
To normal rate (%)	17.24	13.33	0.31	0.7546
Left Achilles tendon				
Exist	25 (86.21 %)	12 (80.00 %)	0.51	0.6115
Weaken or disappear	4 (13.79 %)	3 (20.00 %)		
Total	29	15		
To normal rate (%)	13.79	20	−0.51	0.6115

Table 7 Sixty days after surgery, the results of the sensory test in different groups

	CMC/PEO	Control	Statistics (*Z*)	*P* value
L4 right				
Normal	27 (93.10 %)	13 (86.67 %)	0.67	0.5022
Weaken	2 (6.90 %)	2 (13.33 %)		
Total	29	15		
To normal rate (%)	6.9	13.33	−0.67	0.5022
L4 left				
Normal	26 (89.66 %)	11 (73.33 %)	1.37	0.1715
Weaken	3 (10.34 %)	4 (26.67 %)		
Total	29	15		
To normal rate (%)	10.34	26.67	−1.37	0.1715
L5 right				
Normal	25 (86.21 %)	9 (60.00 %)	1.93	0.054
Weaken	4 (13.79 %)	6 (40.00 %)		
Total	29	15		
To normal rate (%)	13.79	40	−1.93	0.054
L5 left				
Normal	14 (48.28 %)	7 (46.67 %)	0.09	0.9316
Weaken	15 (51.72 %)	8 (53.33 %)		
Total	29	15		
To normal rate (%)	48.28	53.33	−0.30	0.7641
S1 right				
Normal	23 (79.31 %)	14 (93.33 %)	−1.17	0.2411
Weaken	6 (20.69 %)	1 (6.67 %)		
Total	29	15		
To normal rate (%)	20.69	6.67	1.17	0.2411
S1 left				
Normal	26 (89.66 %)	12 (80.00 %)	0.85	0.3933
Weaken	3 (10.34 %)	3 (20.00 %)		
Total	29	15		
To normal rate (%)	6.9	20	−1.26	0.2074

the baseline ODI and VAS scores for lower-back pain and leg pain. No clinically significant changes were detected in laboratory values and vital signs (Tables 6, 7, 8).

In general, all scores improved in both groups at all the time points. In the treatment group, VAS for back pain and leg pain decreased by 76.8 and 90.7 % than the baseline scores. In the control group, VAS for back pain and leg pain decreased by 80.2 and 86.2 %. The ODI scores in treatment and control groups decreased by 77.9 and 79.3 % than the baseline scores, respectively.

At the 30-day time point, the ODI scores in the treatment group decreased by 16.3 % ($P = 0.0007$) than in the control group. The VAS scores for both lower-back pain and leg pain decreased by 9.9 % ($P = 0.0302$) and 27.0 % ($P = 0.0002$) than those in the control group.

At the 60-day time point, the ODI scores further decreased and VAS scores for both lower-back pain and leg pain decreased in both groups. But these differences in scores at 60 days were attenuated. The patients who received PEO/CMC Gel had lower VAS scores by 4.5 % ($P = 0.0149$) for leg pain than the control patients. However, no significant difference was detected between two groups on the ODI and VAS scores for back pain. But the relative values from baseline in ODI and VAS scores for back pain were not significant at 60 days in the treatment group.

Discussion

Carboxymethylcellulose/polyethylene oxide gel is a flowable gel. The gel is a sterile, absorbable, combination of polyethylene oxide (PEO) and sodium carboxymethylcellulose (CMC). In a literature review, CMC is known to be tissue adherent, and PEO, which inhibits protein interactions. Previously, a film composed of CMC and PEO was shown to reduce peritoneal adhesions in a rabbit model [23]. Rodgers reported in an animal study that CMC/PEO gel reduced epidural fibrosis and did not impair normal healing. In a pilot clinical study, Kim applied CMC/PEO gel in lumbar disc herniation patients and assessed the clinical outcomes by self-assessment questionnaire and MRI evaluations. By 90-day follow-up, he found Oxiplex/SP Gel was easy to use and safe for patients undergoing unilateral discectomy [25]. Greater benefit in clinical outcome measures was seen in gel-treated patients, especially those with severe leg pain and weakness at baseline. However, the gold standard questionnaires, such as ODI and VAS, were not used in this study. To evaluate the clinical outcome more intensive, the current single-blind, multi-center, randomized study was carried out in Chinese population. The results showed that PEO/CMC gel was safe for patients, without any clinically measurable adverse event.

Patients using PEO/CMC gel acquired better ODI and VAS scores for lower-back pain and leg pain at the 30-day time point. The ODI and VAS scores for lower-back pain and leg pain both further decreased at the 60-day time point. Although no significant difference was detected on ODI and VAS scores for lower-back pain, the VAS scores for leg pain significant decreased in the PEO/CMC gel group. The reason for lower-back pain is multi-factorial, including lumbar disc disease, lumbar spondylolisthesis,

Table 8 Sixty days after surgery, the results of straight leg raising test in different groups

	CMC/PEO	Control	Statistics (*Z*)	*P* value
Negative	2 (6.90 %)	0 (0.00 %)	0.99	0.3198
Single-side positive	27 (93.10 %)	15 (100.00 %)		
Double-sided positive	0 (0.00 %)	0 (0.00 %)		
Total	29	15		
To normal rate (%)	93.1	100	−0.99	0.3198

myofascial pain, psychosocial factors, as well as muscle damages associated with operation. And PEO/CMC gel was applied on dura and nerve root just to minimize the epidural fibrosis. Thus, in this study, the VAS scores for lower-back pain and ODI which mainly reflect the lumbar conditions did not improve as significantly as VAS scores for leg pain did. This result can also confirm that CMC/PEO gel is able to reduce never root adhesions.

There are some limitations in the current study. First, the follow-up time is not long enough. Although soft tissue healing has completed within almost 8 weeks, epidural fibrosis process may still continue for several months [24]. Therefore, further follow-up to prove the effectiveness of CMC/PEO gel is necessary. Second, no postoperative radiological images were used to evaluate the epidural fibrosis because of the financial burden of patients. Third, due to the limitations of the various objective factors, this study follow-up time is shorter, which may affect the accuracy of the data. Nevertheless, the results of this study suggest that CMC/PEO gel can play a good role in improving the clinical outcomes in patients with laminotomy.

Conclusions

Carboxymethylcellulose/polyethylene oxide gel can play a good role in improving clinical outcomes and reducing the suffering of patients. CMC/PEO gel shows non-toxic side effects.

Conflict of interest Medtronic, Inc., provided the CMC/PEO gel for this study and a grant to offset study costs. Department of Orthopaedics, Xijing Hospital and Peking University Third Hospital have no financial or marketing interest in the materials or methods used, or in any of the manufacturers mentioned in this report. None of the authors own Medtronic stock.

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