SPINE Volume 33, Number 16, pp 1762–1765

Use of Carboxymethylcellulose/Polyethylene Oxide Gel in Microdiscectomy With Interlaminectomy

A Case Series Comparison With Long-term Follow-up

Roberto Assietti, MD,* Annarita Mora, MD,† and Marco Brayda-Bruno, MD‡

Study Design. A consecutive, case series comparison.

Objective. To compare safety, long-term pain, and disability scores with and without use of carboxymethylcellulose/polyethylene oxide (CMC/PEO) gel after microdiscectomy with interlaminectomy.

Summary of Background Data. Patient outcomes after microdiscectomy for lumbar disc herniation are frequently complicated by adhesions and fibrotic scars. Present management is controlled by good surgical technique as adhesion-reduction agents to date, have either proved ineffective or toxic. In 2002 a 100% synthetic combination of CMC/PEO, which reduces adhesions and fibrosis, became available across Europe as a gel application, (OXIPLEX/SP adhesion barrier gel FzioMed, Inc., San Luis Obispo, CA) and distributed under the trade names OXIPLEX/SP adhesion barrier gel (DePuy International, Ltd., Leeds, United Kingdom) and MEDISHIELD adhesion barrier gel (Medtronic International Trading SARL, Tolochenaz, Switzerland).

Methods. A consecutive series of 70 patients with lumbar disc herniation undergoing microdiscectomy with interlaminectomy by the same surgeon were treated at the end of surgery with either CMC/PEO gel (N = 35) or no gel (N = 35). Treatments were allocated by an independent investigator. At presurgery and regular intervals over 3 years postsurgery, Oswestry disability index (ODI) and leg and back pain scores determined by visual analog scales (VAS), were assessed by a member of the surgical team blinded to the initial treatment allocation.

Results. Three years postsurgery reduction in disability as measured by the decrease in ODI compared with presurgery (mean ± SD) was significantly ($P < 0.05$) greater with CMC/PEO than controls (−49.4 ± 12.7 *vs.* −41 ± 17.8). CMC/PEO treatment also resulted in significantly more patients having no disability as measured by reaching 0% ODI scores (15 CMC/PEO [43%] *vs.* 0 control group [0%]) ($P < 0.01$). Leg and back pain as measured by the decrease in VAS scores 3 years postsurgery were reduced with CMC/PEO compared with controls (leg −6.8 ± 1.7 *vs.* −5.6 ± 1.6, back −0.4 ± 1.5 *vs.* −0.1 ± 2.0), $P < 0.05$ for leg pain. Importantly there were no safety issues and no differences in complications between the 2 treatment groups during the 30 day postoperative period.

Conclusion. CMC/PEO gel after microdiscectomy with interlaminectomy appears safe to use and in a 3-year follow-up significantly reduces disability and leg pain scores compared with our conventional treatment.

Key words: microdiscectomy, laminectomy, adhesions, fibrosis, pain, carboxymethylcellulose, polyethylene. **Spine 2008;33:1762–1765**

Microdiscectomy with laminectomy are the most common surgical treatments for lumbar disc herniation and spinal stenosis, but it is estimated that between 3% and 19%[1–3] of cases result in recurrent lumbar disc herniation and instability and pain. The cause of postlaminectomy pain has been controversial,[4,5] but it is now recognized that reduction of epidural adhesions and fibrosis at the attendant spinal nerve and nerve root, as demonstrated by postoperative magnetic resonance imaging (MRI) or computed tomography (CT), can lead to improved outcomes. To date, methods to reduce adhesions and fibrosis have primarily focused on improved surgical technique rather than use of devices which have either proved limited in their effectiveness or toxicity.

More recently the development of modern technologies such as carboxymethylcellulose (CMC) and polyethylene oxide (PEO), which have respectively been shown to reduce adhesions[6–8] and to interact with the proteins causing fibrosis[9] has given surgeons hope that postlaminectomy outcomes can be improved. However, a practical problem with CMC is that it is rapidly resorbed and consequently does not reside at the site of surgery long enough to take effect. This issue has been overcome by development of a 100% synthetic combination of CMC/PEO stabilized with calcium chloride that became available across Europe in 2002 as a gel application, OXIPLEX/SP adhesion barrier gel (FzioMed, Inc., San Luis Obispo, CA) – distributed under the trade names OXIPLEX/SP adhesion barrier gel (DePuy International Ltd., Leeds, United Kingdom) and MEDISHIELD adhesion barrier gel (Medtronic International Trading SARL, Tolochenaz, Switzerland). Assessment of the CMC/PEO in an animal model demonstrated a reduction in epidural fibrosis.[10] A pilot clinical study indicated safety profiles similar to surgery alone and in patients with significant leg pain and lower extremity weakness at baseline, those treated with

From the *Division of Neurosurgery, Ospedale Fatebenefratelli e Oftalmico, Corso di Porta Nuova 23, 20121 Milano, Italy; †Division of Neurosurgery, I.R.C.C.S Ospedale Policlinico, Via Francesco Sforza, 55, 20121 Milano, Italy; and ‡III Division of Spinal Surgery, I.R.C.C.S., Via R. Galeazzi, 4, 20161 Milano, Italy.

Acknowledgment date: November 13, 2007. Acceptance date: February 18, 2008.

The device(s)/drug(s) is/are FDA-approved or approved by a corresponding national agency for this indication.

No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

This assessment was approved by the local ethical committee.

Address correspondence and reprint requests to Roberto Assietti, MD, Division of Neurosurgery, Ospedale Fatebenefratelli e Oftalmico, Corso di Porta Nuova 23, 20121 Milano, Italy; E-mail: roberto.assietti@fastwebnet.it

Table 1. Patient Demographics, History, and Surgery Level of Discectomy

	CMC/PEO	Control
No. patients	35	35
Gender (female/male)	27/8	30/5
Age yrs (range)	54.8 (58–72)	57.1 (24–73)
Mean (SD) duration of symptoms (wks)	16.9 (14.5)	18.3 (14.7)
Type of disc (free fragment/intraforaminal/contained)	20/4/11	5/15/5
Neurology (motor/radicular)	17/18	13/22
Previous discectomy	10	0
Surgery level (L3–L4/L4–L5/L5–S1)	3/12/20	4/13/18

CMC/PEO had a general improvement in outcome throughout the 6-month follow-up.[9]

We were interested in evaluating the safety and efficacy of this gel to reduce postoperative pain and disability, particularly in those patients with recurrent disc herniation, a group, who in our experience have a poorer functional outcome.

Materials and Methods

This assessment was approved by the local ethical committee. Between January and December 2003, a consecutive series of patients undergoing microdiscectomy with interlaminectomy were randomized by an independent member of the surgical team to either surgery plus treatment with CMC/PEO gel or control treatment with surgery alone (no gel), except for those with recurrent herniation who were allocated to the CMC/PEO group on ethical grounds. On completion of 35 patients with CMC/PEO, all other patients in the series without recurrent disc herniation were allocated surgery alone until the 2 group numbers balanced, and 70 patients had completed surgery.

Before surgery, all patients presented with back pain irradiated to the lower extremity and demonstrated a positive Lasegue sign. Before surgery, patients undertook an Oswestry disability index (ODI) assessment and scored leg and back pain using a 10-point visual analogue scale (VAS). Demographics, patient history, and site of surgery performed are summarized by treatment group in Table 1. There was no significant difference between groups except in the number of patients presenting with a previous discectomy in the CMC/PEO treatment group ($P < 0.01$). This patient subgroup had slightly higher presurgery ODI and VAS pain scores than the newly diagnosed herniation subgroup (ODI 55.0 ± 8.8 *vs.* 52.7 ± 13.7, VAS leg 8.0 ± 14 *vs.* 7.6 ± 1.6 and VAS back 3.2 ± 1.5 *vs.* 1.6 ± 1.4) however, these differences were not significant. Furthermore no significant difference was found between the baseline disability and pain scores for each of these 2 subgroups compared with the newly diagnosed controls. It was therefore deemed valid to compare the combine of the 2 subgroups in the CMC/PEO treatment group and compare these with the control treatment. T1

All patients underwent routine follow-up at 30 days, 3 and 6 months. At 1, 2, and 3 years after surgery all patients underwent repeat ODI and VAS leg and back pain scores by a surgical team member unaware of initial treatment allocation. No patients were lost to follow-up, which reflects the limited number of patients included in the study and the simplicity of the follow-up evaluation.

Statistical comparisons between groups and subgroups at baseline were performed using χ^2 or t tests. Comparisons between treatment groups of changes in ODI and VAS leg and back pain to presurgery were assessed using one-way analysis of variance.

Results

The gel was found to be simple to apply, using the supplied syringe and required minimal additional surgical time. At the 30-day postoperative clinical assessment no difference in complication rate or adverse events were observed between the CMC/PEO treated group and the control group. In the CMC/PEO group there was 1 case of delayed wound healing compared with 2 cases in the control group and there were 2 cases of late resolution of sciatica in both groups, but none of these patients had a residual or recurrent disc herniation and the symptoms resolved within the first 2 months. This good safety profile appeared to be maintained 3 years postsurgery. Clin-

Table 2. Mean Disability and Pain Scores Presurgery and Changes 1, 2, and 3 yr Postsurgery – Patients With 0% ODI

			Mean ± SD Change Postsurgery			
Outcome	N	Mean ± SD Presurgery	1 yr	2 yr	3 yr	Treatment Difference at 3 yr
ODI						
CMC/PEO	35	53.4 ± 12.4	−46.6 ± 13.3	−48.7 ± 12.9	−49.4 ± 12.7	$P < 0.05$
Control	35	53.5 ± 14.5	−41.9 ± 15.4	−42.3 ± 15.6	−41.0 ± 17.8	
VAS leg pain						
CMC/PEO	35	7.7 ± 1.5	−6.6 ± 1.9	−6.8 ± 1.8	−6.8 ± 1.7	$P < 0.01$
Control	35	7.6 ± 1.5	−5.7 ± 1.6	−5.6 ± 1.6	−5.6 ± 1.6	
VAS back pain						
CMC/PEO	35	2.0 ± 1.6	−0.3 ± 1.2	−0.4 ± 1.4	−0.4 ± 1.5	NS
Control	35	2.0 ± 1.6	−0.1 ± 1.2	−0.1 ± 1.3	−0.1 ± 2.0	
			Count (%)			
			1 yr	2 yr	3 yr	
ODI 0% count						
CMC/PEO	35	0 (0%)	10 (29%)	12 (34%)	15 (43%)	$P < 0.01$
Control	35	0 (0%)	1 (3%)	0 (0%)	0 (0%)	

ical assessments of disability and pain at presurgery and changes from presurgery 1, 2, and 3 years postsurgery for each treatment group are displayed in Table 2. Both groups demonstrated a reduction in disability measured by reductions in ODI and improved leg pain scores as measured by a reduction in VAS scores compared with presurgery at 1, 2, and 3 years, however, the reduction was significantly greater in the CMC/PEO treated group than the control population at 3 years. The small additional reduction in back pain seen with CMC/PEO was not significant between the 2 groups. Of note was the large number of patients (43%) that had no disability as measured by a zero ODI score at 3 years in the CMC/PEO group compared with 0% in the control group ($P < 0.01$). For the 10 patients who had undergone previous discectomy in the CMC/PEO group this proportion with no disability increased to 70%. These patients also achieved good reductions in disability (ODI) and VAS pain scores at 3 years (Mean ± SD; ODI −52.2 ± 10.4, VAS leg pain −7.2 ± 1.4, VAS back pain −0.8 ± 1.7). No patient had a lumbar herniation recurrence in the CMC/PEO treated group. There were 2 recurrences in the control treatment group.

Discussion

Preventing or limiting the development of scar tissue after lumbar discectomy should lead to improved outcomes. Our present surgical practice relies on the use of minimally invasive surgery and meticulous attention to hemostasis to limit this problem,[11] yet we still observe scar tissue in those patients who return to surgery because of herniation recurrence. The use of adhesion-reduction products and fibrosis limiting products have to date resulted in either inconclusive efficacy or toxic events. Such agents and practices have included fat grafts,[12,13] irrigation of the surgical field,[14] administration of steroids or nonsteroidal anti-inflammatory drugs (NSAIDs),[15,16] or application of hemostatic agents.[17] Low-dose radiotherapy can also reduce the extent of peridural fibrosis in recurrent disc herniation.[18] Among surgical technique variations, the preservation of the ligamentum flavum seems beneficial in reducing epidural scar tissue.[19] A number of synthetic materials have also been tested as ways to control epidural fibrosis after lumbar disc surgery,[20,21] however, none has proved really effective in clinical practice. The only synthetic material that demonstrated clinical effectiveness is a gel of water-soluble sugars (GT 1587 [ADCON-L]; Gliatech, Cleveland, OH and since 2003 Wright Medical technologies Inc., Arlington, TN) and this material is no longer commercially available as several reports indicated that there was a risk of cerebrospinal fluid leakage.[22–24] Given these experiences, the observation in this case series that CMC/PEO appears safe to use, both in the short-term and long-term is encouraging; but clearly extensive device vigilance is still required. The potential long-term outcome benefits observed in this study expand on the initial pilot study data with CMC/PEO[9] and are echoed in recent presentations of other investigator-led studies in Europe.[25,26]

Because there is no evidence that the product is biologically active, the reduction of postoperative adhesions is hypothesized to be through the physical barrier action of the gel between the dural sheet and the surrounding tissues.

Although, in our study neither the surgeon nor the surgery staff was blinded to the treatment, the patient assessments were undertaken by an independent member of the surgical team, and the results clearly indicate that use of CMC/PEO has long-term benefits compared with current practice. This not only has benefits for the patients but may also reduce the hospital burden of revisions for scar tissue related pain. In conclusion, the findings of our case series support further research with this product. Large scale randomized controlled trial designs with radiologic assessment and disability and pain outcomes are warranted.

Note: CMC/PEO (OXIPLEX) is undergoing research in the USA but is not currently licensed by the FDA.

Key Points

- Carboxymethylcellulose/Polyethylene oxide (CMC/PEO) is a synthetic gel which reduces epidural adhesions and fibrosis.
- 70 patients undergoing microdiscectomy with interlaminectomy were treated with either CMC/PEO or nothing (controls).
- Three years postsurgery there was a significantly greater decrease ($P < 0.05$) in Oswestry Disability Index and Visual Analogue Scale leg pain with CMC/PEO than controls.
- Adverse events during the 30-day postsurgery period were comparable.
- Use of CMC/PEO in our surgery improves outcomes and appears safe to use.

Acknowledgments

The authors thank Alison Crowe and Alastair Knight from Corvus Communications Ltd. for their assistance in writing this case series. Corvis received financial support from FzioMed Inc.

References

1. Abromovitz JN, Neff SR. Lumbar disc surgery: results of the prospective lumbar discectomy study of the joint section on disorders of the spine and peripheral nerves of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. *Neurosurgery* 1991;29:301–8.
2. Atlas SJ, Deyo RA, Keller RB, et al. The Maine Lumbar Spine Study, Part II. 1-year outcomes of surgical and nonsurgical management of lumbar spinal stenosis. *Spine* 1996;21:1777–86.
3. Aydin Y, Ziyal IM, Duman H, et al. Clinical and radiological results of lumbar microdiskectomy technique with preserving of ligamentum flavum comparing to the standard microdiskectomy technique. *Surg Neurol* 2002; 57:5–13.
4. Benoist M, Ficat C, Baraf P, et al. Postoperative lumbar epiduro-arachnoiditis. Diagnostic and therapeutic aspects. *Spine* 1980;5:432–6.

5. Boden SC, Wiesel SW. The multiply operated low back patient. In: Rothman, Simeone, eds. *The Spine* 3rd ed. Philadelphia: Saunders; 1992:1899–1906.
6. Kitano T, Zerwekh JE, Edwards ML, et al. Viscous carboxymethylcellulose in the prevention of epidural scar formation. *Spine* 1991;16:820–3.
7. Elkins TE, Bury RJ, Ritter JL, et al. Adhesion prevention by solutions of sodium carboxymethylcellulose in the rat. *I. Fert Steril* 1984;41:926–8.
8. Fredericks CM, Kotry I, Holtz G, et al. Adhesion prevention in the rabbit with sodium carboxymethylcellulose solutions. *Am J Obstet Gynecol* 1986; 155:667–70.
9. Kim KD, Wang JC, Robertson DP, et al. Reduction of leg pain and lower-extremity weakness with Oxiplex/SP gel for 1 year after laminectomy, laminotomy, and discectomy. *Neurosurg Focus* 2004;17:1–6.
10. Rodgers KE, Robertson JT, Espinoza T, et al. Reduction of epidural fibrosis in lumbar surgery with Oxiplex adhesion barriers of carboxymethylcellulose and polyethylene oxide. *Spine J* 2003;3:277–84.
11. Touliatos AS, Soucacos PN, Beris AE. Post-discectomy perineural fibrosis: comparison of conventional versus microsurgical techniques. *Microsurgery* 1992;13:192–4.
12. Bryant MS, Bremer AM, Nguyen TQ. Autogeneic fat transplants in the epidural space in routine lumbar spine surgery. *Neurosurgery* 1983;13:367–70.
13. Van Akkerveeken PF, Van de Kraan W, Muller JW. The fate of the free fat graft. A prospective clinical study using CT scanning. *Spine* 1986;11:501–4.
14. Hoyland JA, Freemont AJ, Denton J, et al. Retained surgical swab debris in post-laminectomy arachnoiditis and peridural fibrosis. *J Bone Joint Surg Br* 1988;70:659–62.
15. He Y, Revel M, Loty B. A quantitative model of post-laminectomy scar formation. Effects of a nonsteroidal anti-inflammatory drug. *Spine* 1995;20: 557–63.
16. Minamide A, Tamaki T, Hashizume H, et al. Effects of steroid and lipopolysaccharide on spontaneous resorption of herniated intervertebral discs. *Spine* 1998;23:870–6.
17. Cooper RG, Mitchel WS, Illingworth KJ, et al. The role of epidural fibrosis and defective fibrinolysis in the persistence of postlaminectomy back pain. *Spine* 1991;18:1044–8.
18. Gerszten PC, Moossy JJ, Flickinger JC, et al. Low-dose radiotherapy for the inhibition of peridural fibrosis after reexploratory nerve root decompression for postlaminectomy syndrome. *J Neurosurg* 2003;99 (3 suppl):271–7.
19. Ozer AF, Oktenoglu T, Sasani M, et al. Preserving the ligamentum flavum in lumbar disectomy: a new technique that prevents scar tissue formation in the first 6 months postsurgery. *Neurosurgery* 2006;59 (suppl 1):ONS126–33.
20. DiFazio FA, Nichols JB, Pope MH, et al. The use of expanded polytrafluorethylene as an interpositional membrane after lumbar laminectomy. *Spine* 1995;20:986–91.
21. Mohsenipour I, Daniaux M, Aichner F, et al. Prevention of local scar formation after operative discectomy for lumbar disc herniation. *Acta Neurochir* 1998;140:9–13.
22. Hieb LD, Stevens DL. Spontaneous postoperative cerebrospinal fluid leaks following application of anti-adhesion barrier gel. *Spine* 2001;26:748–51.
23. Kuhn J, Hoffmann B, Knitelius HO, et al. Bilateral subdural haematomata and lumbar pseudomeningocele due to a chronic leakage of liquor cerebrospinalis after a lumbar discectomy with the application of ADCON-L gel. *J Neurol Neurosurg Psychiatry* 2005;76:1031–3.
24. Le AX, Rogers DE, Dawson EG, et al. Unrecognized durotomy after lumbar discectomy: a report of four cases associated with the use of ADCON-L. *Spine* 2001;26:115–17.
25. Fransen P. Safety of carboxymethylcellulose/polyethylene oxide for the prevention of adhesions in lumbar disc herniation—consecutive case series review. *Ann Surg Innov Res* 2008;2:2. Epub available at: http://www.asir-journal.com/content/2/1/2. Accessed June 10, 2008.
26. Agarwal A, Hammer AJ. Antiadhesion barrier gel improves clinical outcome in lumbar discectomy patients: a prospective randomized trial of oxiplex barrier gel. *International Society for the Study of the Lumbar Spine* 2007; Abstract:80.