

EFFICACY OF ANTI-ADHESION GEL OF CARBOXYMETHYLCELLULOSE WITH POLYETHYLENE OXIDE ON PERIPHERAL NERVE: EXPERIMENTAL RESULTS ON A MOUSE MODEL

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ABSTRACT: *Introduction:* Perineural scar formation is responsible for pain and loss of function after surgical procedures. Neurolysis and application of anti-adhesion gels are required to restore a gliding surface. We tested a carboxymethylcellulose (CMC) and polyethylene oxide (PEO) gel on mouse sciatic nerve to describe its safety and efficacy. *Methods:* Adult mice underwent a surgical procedure in which we burned the muscular bed of the sciatic nerve bilaterally (Burned group) and applied anti-adhesion gel to 1 of the nerves (Burned+gel group). After 3 weeks, we studied scar tissue by biomechanical and histological evaluation. *Results:* Both histological and biomechanical analysis showed that the gel reduced perineural scarring. The difference between the Burned and Burned+gel groups was statistically significant. *Conclusions:* CMC-PEO gel can reduce perineural scar tissue. In histological section, scar tissue was present in both groups, but in the Burned+gel group a gliding surface was identified between scar and nerve.

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Scar tissue formation between nerve and surrounding muscle is one of the most undesired occurrences in nerve surgery. Perineural scar tissue is responsible for recurrent compressive syndrome,¹ both in the peripheral nervous system (PNS) and the central nervous system (CNS) (e.g., nerve roots).^{2,3} In the PNS, perineural fibrosis is the second most frequent cause of recurrent carpal tunnel syndrome (CTS).^{4,5} Patients with recurrent CTS often must undergo re-operation owing to debilitating symptoms that affect daily activity. The most frequent pathologies connected with this condition are traction neuropathies⁶ and type II Complex Regional Pain Syndrome.⁷ To prevent complete loss of function, it is essential to perform external neurolysis and then apply a gliding barrier to the affected nerve. Vascularized tissue works well as a gliding barrier, but harvesting local or free flaps is difficult and complications have been described.⁸ An alternative is to cover the treated

Abbreviations: CMC, carboxy-methylcellulose; CNS, central nervous system; CTS, carpal tunnel syndrome; HA, hyaluronic acid; PE, phosphatidyl-ethanolamine; PEO, poly-ethylene-oxide; PNS, peripheral nervous system

Key words: anti-adhesion gel; CMC-PEO; perineural adherence; peripheral nerve; nerve repair

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nerve with biocompatible gel. These products have been developed and proposed in the last few decades, first in animal models and subsequently in surgical practice.

Initially, anti-adhesion gels were developed from films used in abdominal surgery for prevention of adhesion syndromes.⁹ For peripheral nerve repair, the classical form was not considered appropriate, thus a hydrogel form was developed. The biochemical composition has also been modified; collagen and dextran-sulfate were introduced first,¹⁰ followed by hyaluronic acid (HA), both in experimental models and in clinical practice^{11–14} as Hyaloglide (Fidia Advanced Bio-polymers, Abano Terme, Italy). Recently, several studies have reported using carboxy-methylcellulose (CMC) with phosphatidyl-ethanolamine (PE) or polyethylene oxide (PEO)^{15–17} to improve anti-adhesion capability.

This kind of anti-adhesion gel was previously and successfully used in the CNS as OXIPLEX®/SP Adhesion Barrier Gel (FzioMed, Inc., San Luis Obispo, California) or MEDISHIELD™ Adhesion Barrier Gel (Medtronic International Trading SARL, Tolochenaz, Switzerland) to reduce epidural fibrosis in lumbar surgery¹⁸ and to subsequently reduce pain after laminectomy, laminotomy, or discectomy.¹⁹

The CMC-PEO formulation for PNS was not tested on preclinical *in vivo* models for assessment of its anti-adhesion potential and efficacy, hence, we decided to build a model capable of measuring the efficacy of this gel.

In this study, we tested the efficacy of Dynavisc® (FzioMed, Inc.), a CMC-PEO gel for reduction of perineural scar tissue formation in a mouse model by evaluating the peak pull out force²⁰ and histological aspects of the muscle–nerve interface, before and after gel application on an injured sciatic nerve model following methods described previously.²⁰

MATERIALS AND METHODS

All procedures were performed in accordance with the Local Ethics Committee and the European Communities Council Directive of EU/63/



FIGURE 1. (a) Gluteal splitting incision to expose the sciatic nerve. (b) Burning of the muscular bed surrounding the sciatic nerve. (c) The 1 ml of CMC-PEO gel application after burning of the muscular bed.

2010. To perform our analysis, we used a versatile, common, and cost-effective animal model described recently.²⁰

Animal and Experimental Groups. Twenty-six Crl:CD1 (ICR) adult mice (5 weeks old, average weight 28 g, Charles River Laboratories, Calco, Lecco, Italy) were anesthetized using a combination of 100 mg/kg of Ketamine and 15 mg/kg of Xylazine given intraperitoneally. Under microscope magnification, both sciatic nerves were exposed by gluteal splitting incisions to expose the sciatic nerve from the gluteal vein to the trifurcation as shown in Figure 1a.

We randomly divided all sciatic nerves into 3 experimental groups: (1) the Burned group, (2) the Burned + CMC-PEO anti-adhesion gel group, and (3) the Control group.

In the Burned group (17 nerves), after retraction of the nerve, we burned the muscle surface of biceps femoris and vastus lateralis muscles with a diathermocoagulator for approximately 0.8 cm along the nerve bed (Fig. 1b), as described previously.^{11,20,21} In the Burned + anti-adhesion gel group (17 nerves), after muscle burning as described above, we applied a small quantity of gel (1 ml) to the muscular bed to completely cover and surround the nerve as illustrated in Figure 1c. In the Control group (17 nerves), we exposed the sciatic nerve and immediately closed the skin with 3-0 prolene sutures.

The animals were housed under standard light conditions, with unlimited access to food and water. Postoperative analgesia was carried out with Carprofen 5 mg/kg sub-cutis every 12 h. After 3 weeks, all animals were anesthetized following the previous protocol and then killed by cervical dislocation.

Biomechanical Analysis. Biomechanical evaluation was performed in each group. Fourteen nerves from each group were tested biomechanically.

Biomechanical evaluation was performed to measure the peak force required to pull the nerve from the muscular bed using the method and tools described in a previous report.²⁰ Basically, the tool consisted of applying a force continuously to the nerve until the traction breaks up the adhesion between the nerve and the surrounding tissue. A schematic view of the traction tool is shown in Figure 2. The force is reported in Newtons (N). A normality test was performed by the Kolmogorov Smirnov test. Statistical analysis of the results was by Student *t*-tests. Statistical significance was established when $P < 0.05$.

Histological Analysis. Three nerves each for the burned and gel groups and 4 nerves in the control group were evaluated by histological analysis. The posterior space of the thigh with nerve and scar tissue inside the muscles was harvested *en bloc*. The proximal end was marked with 9-0 Nylon. Nerves were fixed with 4% paraformaldehyde (Fulka) in

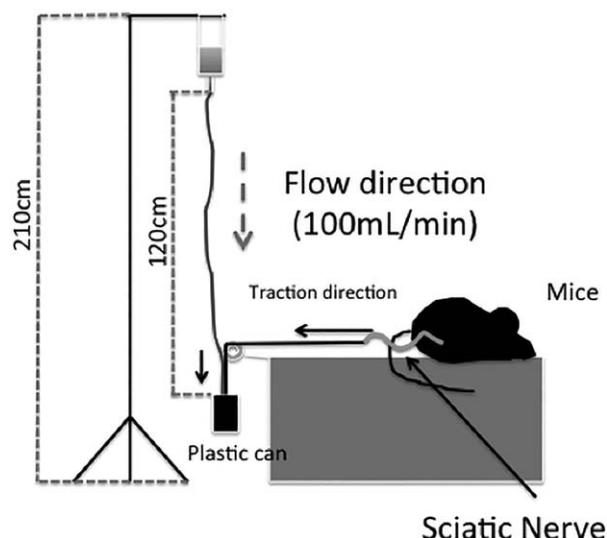


FIGURE 2. Schematic view of biomechanical evaluation tool. We measured the peak pull out force needed to detach the nerve from the muscular bed. The peak pull-out force corresponds to scar toughness.

Table 1. Biomechanical results.*

Sample	Burning + gel	Control	Burning
1	0.37	0.28	0.41
2	0.45	0.38	0.55
3	0.49	0.26	0.40
4	0.31	0.32	0.49
5	0.35	0.29	0.52
6	0.41	0.24	0.52
7	0.46	0.31	0.46
8	0.32	0.32	0.37
9	0.28	0.32	0.44
10	0.38	0.38	0.54
11	0.39	0.34	0.58
12	0.33	0.25	0.37
13	0.31	0.19	0.37
14	0.31	0.37	0.36
Mean	0.37	0.30	0.46
SD	0.06	0.06	0.08

*Peak pull out force values in N for each group with mean and standard deviation.

phosphate buffered saline (PBS) for 2–4 h followed by washing in 0.2% glycine in PBS. After fixation, samples underwent dehydration in ethanol from 50% to 100%, followed by a dyaphanization step in xylol. Specimens were maintained in liquid paraffin at 60°C overnight and then passed to a second step in liquid paraffin at 60°C before polymerization at room temperature.²² After paraffin embedding, transverse sections (10 µm thickness) were obtained and stained with Picosirius staining (picric acid + Sirius red) according to a previously described protocol.²³ Sirius Red stains collagen I and III fibers and emphasizes connective tissue that appears in red in histological sections. No statistical analysis was conducted on these samples.

RESULTS

Biomechanical Analysis. Table 1 lists all peak pull out force values for each nerve. The results of biomechanical analysis are summarized in Figure 3 as the mean force, in N, necessary to tear the nerve from muscle. The Burned group had the highest resistance to traction (mean 0.45 N). After gel application, peak pull out force decreased to 0.37 N. The Control group had the lowest traction values (0.3 N). The Kolmogorov Smirnov Test for normality was applied in each group with $P > 0.15$, thus all groups had a normal distribution. The *t*-test showed a statistical difference between the control and burned groups (Burned group vs. Control group, $P = 2 \times 10^{-6}$). This comparison demonstrates the efficacy of our method to induce scarring. The statistical analysis also shows a difference between the burned group and the gel group (Burned + anti-adhesion gel group vs. Burned group, $P = 0.003$) demonstrating the capacity of

the gel to reduce scarring induced by burning injury.

Histological Analysis. Histological analysis of the mouse sciatic nerve showed different patterns of scar tissue formation. In the Control group, no pathological scar tissue was detectable (Figs. 4a and 5a). In sections from the Burned group (Figs. 4b and 5b), the perineural scar was tightly connected to muscle and penetrated the epimysium with spicules that reached and surrounded muscle cells. In this way, the nerve was undetectable from the surrounding tissue. In the Burned + anti-adhesion gel group (Figs. 4c and 5c), a thinner scar layer was present compared with the Burned group. Scar tissue did not penetrate surrounding muscle, allowing the nerve to glide easily on the muscular bed.

DISCUSSION

In this study, we have described the anti-adhesion potential of CMC-PEO gel (Dynavisc®, FzioMed, Inc) in the PNS. The need to provide nerves with a gliding surface is well known owing to their excursion during limb movement, as demonstrated by *ex vivo* studies.^{24,25} Scar tissue limits this physiological property and leads to chronic ischemia of the nerve and intraneuronal scar formation that is responsible for traction neuropathy.⁶

Many authors have proposed different ways to obtain nerve protection and gliding by using local soft tissues, such as vein wrapping,²⁶ local adipose or muscle flap,^{27–29} or a free omental flap.³⁰ But these procedures require the skills of an experienced surgeon. Moreover, in the case of mild fibrous compression, the authors of a recent publication⁸ proposed external neurolysis and

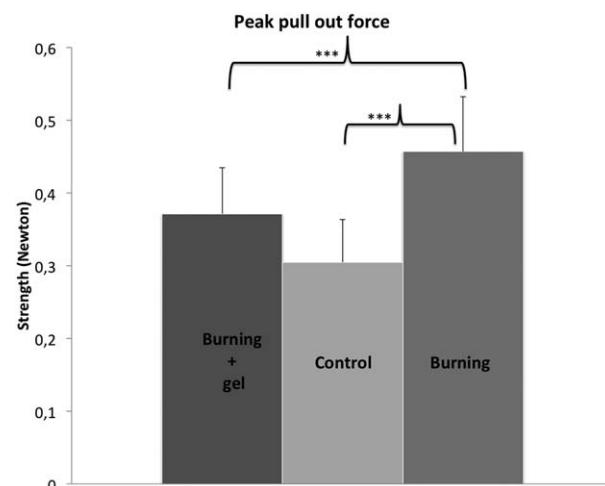


FIGURE 3. Peak pull out force for the 3 groups. After CMC-PEO gel application, there was a significant reduction in scar tissue toughness (0.37 N in CMC-PEO gel group vs. 0.45 N in the Burned group). *** $P \leq 0.001$.

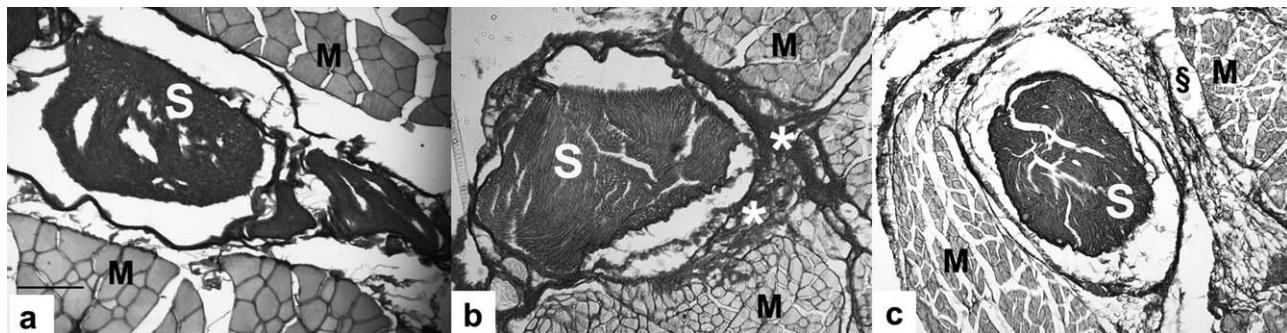


FIGURE 4. Histological view of transverse section of *en bloc* specimens (Sirius Red Stain). Sections at 10 \times magnification show normal appearance of sciatic nerve (S) and surrounding muscles (M) without pathological scar tissue (**a**). After burning of the muscle bed (**b**), scar tissue is identifiable (*). After CMC-PEO gel application on the burned muscle bed (**c**), scar tissue is also appreciable (*), but it is thinner than in (b) and is separate from the epineurium. A cleavage plane (§) is identifiable between scar tissue and epineurium, which allows free gliding of nerve during limb movement and confirms the biomechanical evaluation results

application of anti-adhesion gels, which is easier and quicker than tissue coverage.

These gels have been proposed since the 1970s. Initial studies were focused on spinal root scar prevention.^{2,3} Subsequent preclinical studies have been conducted on peripheral nerves,³¹ as perineural scar formation is a frequent cause of peripheral nerve surgery failure¹ and is responsible for recurrent compression.

The first biocompatible gel used in experimental models was ADCON-T/N®, which is composed of collagen and dextran-sulfate¹⁰; those findings have been confirmed by clinical studies on peripheral nerves.¹⁴ However, cases of cerebrospinal fluid leakage have been reported following use of carbohydrate polymer gel in spinal surgery.

The next step in perineural scar prevention was focused on finding gels that avoided healing problems. Carboxy-methylcellulose with phosphatidyl-ethanolamine (CMC-PE),^{15–17} a nonionic water-soluble polymer that improves surface gliding, has been subsequently used.^{32,33}

In peripheral nerve surgery, CMC was initially used as a film³⁴ with good results, including scar prevention, on rabbit sciatic nerve. There is much evidence about the efficacy of CMC, whether alone

or used in combination with HA in animal models.¹¹

Another effective combination of CMC is with PEO, initially as an anti-adherence compound in vertebral surgery as Oxiplex® Bioabsorbable Gel® (FzioMed Inc) and then applied to an animal model of nerve injury by Yamamoto et al.¹⁵ with evidence of gliding properties.

Biochemically, sodium carboxy-methylcellulose is a high molecular weight polysaccharide polymer that is water soluble, biocompatible, heat stable, and available in various molecular weights and viscosities.³⁵ PEO is a nonionic, water soluble polymer widely used for stabilizing colloids and for formulating pharmaceutical products. Fibrin and fibrin gel matrix do not interact well with PEO, limiting interaction between opposing surfaces; in particular, PEO inhibits protein deposition on tissue surfaces.^{36,37}

The combination of CMC and PEO gel acts as a CMC-carboxylate-calcium-chloride ion complex, which provides the interaction between CMC and PEO and ultimately determines the rheology, tissue adherence, and residence time.

In this study, we did not observe any reaction during or after surgery, demonstrating the

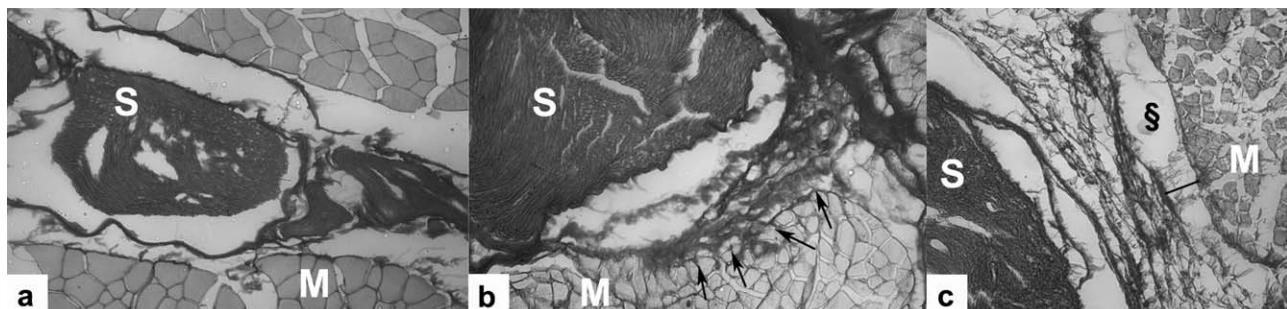


FIGURE 5. Histological view of transverse section of *en bloc* specimens (Sirius Red Stain). Sections at 20 \times magnification are shown. In burned sections (**b**), collagen fiber spiculae (→) tightly connect the nerve to surrounding tissue. In the control slice (**a**), no scar tissue appears between muscle and nerve. After gel application (**c**), a cleavage plane (§) is clearly identifiable between scar tissue and epimysium. The cleavage plane is marked with a vertical bar (-). Scale bar = 30 μ m.

biocompatibility and safety of the product. Our model clearly shows a reduction in scar tissue formation between the different layers forming the nerve and the muscle around it. Both histological and mechanical tests were performed. The latter tests demonstrate the mechanical barrier of CMC as proposed in a previous study.¹⁸ We did not find any adverse effect of this gel.

However, there are some limitations to our study. We did not test functional impairment and recovery after gel application, because motor impairment is a late occurrence. Our findings should be confirmed with more randomized trials focused on the symptomatology. Moreover, our study did not clarify the biomechanical activity of CMC as proposed by different authors.^{18–40} A future option could focus on the reason for inhibition of the activity of the macrophages.

In conclusion, we applied CMC-PEO anti-adhesion gel to a burned perineural muscle bed with extensive scar tissue and performed both biomechanical and histological analysis. The quantitative evaluation showed a clear and statistically significant reduction in scar tissue after gel application compared with the Burned group. The qualitative (histological) analysis supported the biomechanical findings depicting the pattern of scar tissue.

This study proves the efficacy of this new CMC-PEO gel in the prevention of scar tissue formation in an animal model, and shows the safety and biocompatibility of this product. Additional clinical studies are required to evaluate gel efficacy on functional impairment, and further biomolecular investigations are needed to understand mechanics of action of CMC-PEO.

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