CLINICAL EVALUATION OF A HYALURONAN-BASED GEL FOLLOWING MICROSURGICAL RECONSTRUCTION OF PERIPHERAL NERVES OF THE HAND

ANDREA ATZEI, M.D.,[1*] MAURIZIO CALCAGNI, M.D.,[2] BRUNO BREDA, M.D.,[3] GIAMPAOLO FASOLO, M.D.,[3] GIORGIO PAJARDI, M.D.,[2] and LANDINO CUGOLA, M.D.[1]

A controlled clinical trial was performed to investigate the safety and efficacy of the hyaluronate-based gel polymer Hyaloglide® after microsurgical reconstruction of peripheral nerves of the hand. Thirty patients were randomized to receive either no postsurgical treatment ($n = 16$) or Hyaloglide® ($n = 14$) and were clinically evaluated at various intervals for 1 year. The application of Hyaloglide® posed no safety concerns. Efficacy was assessed by the recovery of sensitivity, measurement of pain, and progression of Tinel's sign. The Hyaloglide®-treated group showed better improvement in recovery from pain, approaching statistical significance during the first 3 months postsurgery. Likewise, recovery of sensitivity was also higher in the Hyaloglide®-treated group throughout the entire follow-up period, and the distance of Tinel's sign was longer in the Hyaloglide®-treated group ($P < 0.05$ at day 30). The application of Hyaloglide® may improve recovery of sensitivity and decrease pain following microsurgical repair of the peripheral nerves of the hand.
© 2007 Wiley-Liss, Inc. Microsurgery 27:2–7, 2007.

During the last decades, considerable progress has been made in understanding the mechanisms of nerve repair, although this has still not been translated into clinically relevant improvements. Surgical intervention for nerve repair would greatly benefit from valid strategies that enhance nerve regeneration and reduce the formation of postoperative adhesions. During healing, sutured nerves must remain free to glide over adjacent structures, and if they become tethered, pain can result and worsen clinical outcome.[1] Accordingly, the application of absorbable barriers, based on biocompatible polymers such as hyaluronan and other glycosaminoglycans that protect and isolate the nerve, would reduce the formation of perineural fibroadhesive scars.

Hyaluronic acid (HA), a natural component of the extracellular matrix in several tissues, has several key roles in wound healing and meets many prerequisites for use in antiadhesion applications. Along these lines, HA has been previously shown to enhance peripheral nerve regeneration and prevent perineural scar formation in an experimental rat model.[2] An HA-carboxymethylcellulose membrane has also been shown to decrease the formation of both intra- and extraneural fibrosis in rabbits.[3]

Hyaloglide® (Fidia Advanced Biopolymers, Abano Terme, Italy) is a crosslinked hyaluronan gel that is both biocompatible and bioreabsorbable, with a degradation pathway equivalent to HA. It also has improved viscoelastic properties compared to unmodified HA solutions of the same molecular weight.[4–6] Hyaloglide® is extremely adherent and has a prolonged residence time prior to reabsorption, which should confer antiadhesive properties during healing.[7–9] A similar product has been shown to be effective in reducing adhesions in gynecologic and intra-abdominal surgery in both experimental and clinical trials.[10–14] Moreover, Hyaloglide® has been shown to reduce postoperative perineural adhesions in animal models.[15,16] Altogether, these characteristics suggested that such a strategy could be applied successfully to the prevention of adhesions following peripheral nerve repair, with the added advantage of improved nerve regeneration.

The aim of the present multicenter, randomized, controlled clinical trial was to investigate the safety, tolerability, applicability, and effectiveness of Hyaloglide® after microsurgical reconstruction (suture or neurolysis) of peripheral nerves of the hand.

MATERIALS AND METHODS

This was a multicenter, randomized, and controlled clinical trial lasting from April 2000 to October 2002. Thirty patients with an average age of 47 years (range 21–77 years) undergoing microsurgical intervention of the peripheral nerves of the hand were enrolled in the study. Microsurgical intervention was either for repair of fresh injuries or revision of previous reconstructive intervention performed within 6 months after trauma. Inclusion criteria included a minimum age of 18 years and the ability to understand and sign an informed consent form. Exclusion criteria included documented or suspect pregnancy, clinically significant pathologies (such as diabetes), documented

[1]Hand Surgery Unit, Policlinico "G.B. Rossi," Azienda Ospedaliera-Universitaria, Verona, Italy
[2]Functional Unit of Hand Surgery, MultiMedica Institute, Sesto S. Giovanni, Milan, Italy
[3]Division of Hand Surgery, Dolo Hospital, Dolo, Venice, Italy
The authors have not received consultant fees from FAB.
Research Grant sponsor: Fidia Advanced Biopolymers (FAB).
*Correspondence to: Andrea Atzei, M.D., Hand Surgery Unit, Policlinico "G.B.Rossi," P.le L.A. Scuro, 10, 37100 Verona, Italy.
E-mail: andrea.atzei@univr.it; andreatzei@libero.it
Received 28 September 2006; Accepted 28 September 2006
Published online 4 January 2007 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/micr.20299

© 2007 Wiley-Liss, Inc.

WILEY InterScience® DISCOVER SOMETHING GREAT

presence of neoplasms, rheumatoid arthritis, or alterations in blood coagulation. The following clinical centers participated in the trial: Center 1, Hand Surgery Unit, University of Verona Hospital, Verona; Center 2, Division of Hand Surgery, Dolo Hospital, Dolo (Venice); and Center 3, Functional Unit of Hand Surgery, MultiMedica Institute, Sesto S. Giovanni (Milan). The study was designed in accordance with the Declaration of Helsinki and was approved by the respective Institutional Review Boards. After obtaining informed consent, patients underwent an initial visit to determine eligibility criteria.

Patients were preoperatively randomized and assigned to the Hyaloglide® or control group according to a random computer-generated list. Patients in the treatment group received postsurgical application of Hyaloglide®, while those in the control group received no postsurgical treatment.

All surgical procedures were performed by hand surgery specialists. Neurolysis or epineural nerve repairs with 9/0–10/0 nylon sutures were carried out using a standardized surgical procedure in an operating theater and in a bloodless field under loupes magnification. Brachial plexus block was used for the majority of patients (70%), followed by local (23%), or general anesthesia (7%). At the end of the surgical procedures, immediately before cutaneous suture, patients randomly assigned to the treatment group underwent application of the Hyaloglide® gel. The device was provided in prefilled 5 ml transparent and sterile syringes. The gel was applied intraoperatively along the repaired nerve. Patients assigned to the control group received no adjunctive treatment. For both patient groups, the region operated upon was immobilized for 3 weeks following surgery and was then followed by a period of gradual, active mobilization involving kinesitherapy.

Six follow-up visits were performed at 10, 30, 60, 90, 180, and 360 days following surgical intervention. At each postsurgical visit, patients were assessed for compliance, concomitant treatments, adverse events, and efficacy parameters. Efficacy was assessed by the recovery of sensibility (criteria established by the British Research Medical Council), measure of pain (Visual Analogic Scale – VAS), and the progression of the Tinel's sign from site of surgery (cm).[17] The recovery of sensibility is scored from 0 to 5 (S0, absence of sensibility in the autonomous area of the damaged nerve; S1, recovery of deep pain sensibility; S2, recovery of some degree of superficial pain and tactile sensibility; S3, recovery of tactile and pain sensibility within the autonomous area; S3+, more advanced stage 3 recovery; S4, complete recovery). Recovery of motor function was evaluated using a score from 0 to 5 (M0, complete paralysis; M1, return of perceptible contraction in the proximal muscles; M2, return of perceptible in both the proximal and distal muscles; M3, return of function in both proximal and distal muscles such that they can act against resistance; M4, stage 3 plus the possibility of synergic and independent movement; M5, complete recovery). Recovery of motor function of the median nerve was assessed using a score from 1 to 3 (M1, abduction of thumb against force and complete flexion of fingers without resistance; M2, complete abduction/opposition of thumb with 50% of pinch and complete flexion of fingers with 50% of hold; M3, normal function of pinch and hold). The number and characteristics of adverse events were also recorded during the entire study period.

Statistical Methods

Statistical analysis was performed using SAS version 8.2. A $P < 0.05$ was considered statistically significant. Homogeneity between the treatment and control groups was assessed by either the *t*-test or Wilcoxon's test, according to normal or non-normal data distribution, applied to continuous data. A χ^2 or Fisher's exact test, as appropriate, was used for dichotomous or categorical data. The normality of the data distribution was assessed using the Shapiro-Wilk test. Unavailable data of efficacy parameters at one visit were replaced by the previous data set according to the last observation carried forward method.

Changes in pain were analyzed by a χ^2 or Fisher's exact test, as appropriate, while changes in the degree of pain were measured as the difference (mm) between postsurgery and baseline, and were analyzed using a *t*-test or Wilcoxon's test, according to the normality or non-normality of data distribution. The degree of pain and its changes from baseline was described setting to zero when the pain was absent, so as not to overlook the information due to the positive evolution of pain.

The remaining efficacy parameters were assessed throughout the postsurgical observation period and were analyzed without any transformation. A *t*-test or Wilcoxon's test, according to the normality or non-normality of data distribution, was used to analyze the distance of Tinel's sign from the site of surgery (cm). Recovery of sensibility and motor functions were analyzed by either a χ^2 or Fisher's exact test.

RESULTS

A total of 30 patients were enrolled in the study, including 20 females and 10 males ranging in age from 21 to 77 years (average 47). Fourteen patients were treated with Hyaloglide® and 16 received no postsurgical antiadhesive treatment. All randomized subjects met the criteria to enter the data analysis phase. Crushing (43%) and guillotine (33%) were more frequent types of lesion. The lesion occurred in the hand zones I (13%); II (23%); III (3%); IV (23%); V (33%); and both IV and V in 1 patient (3%). The most frequently damaged nerve was the median (63%), followed by the collateral (20%), radial (10%), and ulnar

Table 1. Summary of Relevant Clinicopathological Data

	Hyaloglide ($N = 14$)	Control ($N = 16$)	Total ($N = 30$)	P
Male/Female	4/10	6/10	10/20	0.709[a]
Mean age (±SD) (years)	49.1 (17.3)	44.9 (14.0)	46.9 (15.5)	0.477[b]
Type of surgery				
Neurolysis	13	13	26	1.000[a]
Nerve Repair	1	2	3	
Both	0	1	1	
Nerve				
Median	7	8	15	0.208[a]
Collateral	3	8	11	
Other	4	0	4	
Nerve type				
Mixed	8	8	16	0.578[a]
Sensory	5	8	13	
Motor	1	0	1	
Hand Zone[c]				
I	1	3	4	0.749[a]
II	3	4	7	
III	0	1	1	
IV	5	3	8	
V	5	5	10	
Mean days of observation (SD)	309 (123)	321 (93)	315 (106)	0.771[d]

N, number of patients.
[a]*Fisher's test.*
[b]*t-test.*
[c]*As defined by the IFSSH classification for flexor tendon surgery (Amadio P et al. IFSSH Flexor Tendon Committee report. J Hand Surg Br 2005;30:100–116).*
[d]*Wilcoxon's test.*

nerve (7%). Associated lesions were reported for 5 patients (17%). Neurolysis was performed in 87% of patients and nerve repair in 10%; both neurolysis and nerve repair were performed in 1 patient (3%). These results are shown in Table 1.

There were no statistically significant differences between the 2 groups regarding gender, age, or other clinicopathological and surgical parameters. The overall application of Hyaloglide® gel in the surgical site was considered very easy, with good adhesion to the raw surfaces. About 3 ml of Hyaloglide® was applied in the majority of cases (12 patients, 86%), while the remaining 2 cases had only about 1 ml applied. Clinical assessment revealed no differences between the 2 groups with regards to adverse events and there was no evidence of undesirable effects of wound closure at follow-up visits. Only 1 serious adverse event (saphenectomy) was reported in a control patient. Any correlation between treatment with Hyaloglide® and the occurrence of adverse events was excluded in all cases.

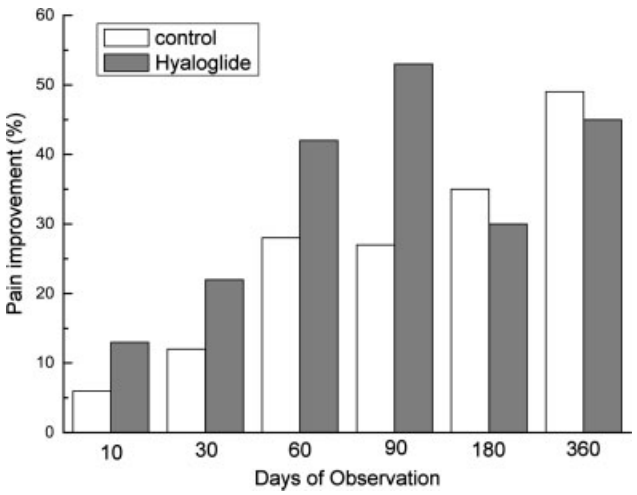

Figure 1. Percent of pain improvement assessed at follow-up visits. The highest percentages of improvement are seen at days 60 and 90 for Hyaloglide, although the difference was not statistically significant.

Assessment of Pain and Motor Recovery

The percentages of the improvement of pain (change from presence of pain at initial visit to absence of pain at postsurgery visit) at each visit are shown in Figure 1. The improvement was higher in the Hyaloglide®-treated group during the first 3 months postsurgery, with a maximal difference seen at day 90. The degree of pain (VAS scale from 0 to 100 mm) as well as its changes from baseline was also measured. The degree of pain itself did not show any significant differences between the two treatment groups. However, when the changes from baseline were compared, the Hyaloglide®-treated group showed notable differences with respect to the control group because of the greater reduction of baseline severity of pain during the first 3 months following surgery. These differences (Fig. 2) approached statistical significance at days 10 ($P = 0.070$), 30 ($P = 0.055$), 60 ($P = 0.060$), and 90 ($P = 0.074$). There were no significant differences in the recovery of motor

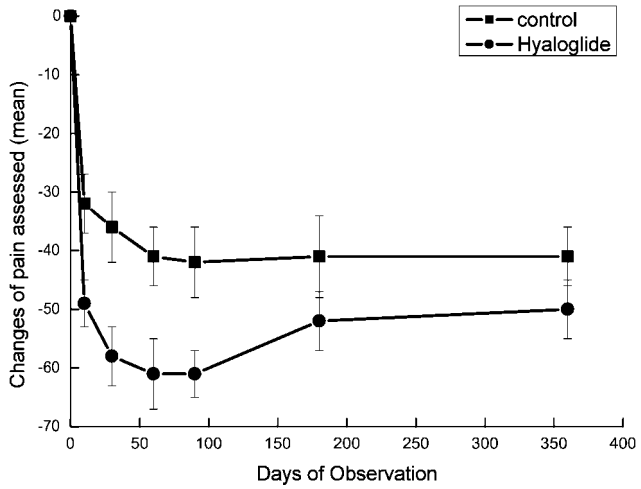

Figure 2. Mean values of changes in the degree of pain assessed by a VAS from baseline during the postsurgical period. Standard deviations are as indicated. A decreasing trend indicates an improvement of pain. Differences nearing statistical significance were seen at days 30 ($P = 0.055$) and 60 ($P = 0.060$).

function between the 2 treatment groups at any follow-up visit.

Recovery of Sensitivity

The recovery of sensitivity was assessed only in patients with lesions involving sensitive or mixed nerves. The frequency distribution in the 5 classes of recovery is shown in Table 2. Although there were no statistically significant differences between the 2 groups, it is of interest that the percentage of full recovery of sensitivity was higher in the Hyaloglide®-treated group throughout the entire follow-up period and was more pronounced at earlier times. The mean values at each follow-up visit are shown in Figure 3. Although the differences between the 2 groups were not statistically significant, the Hyaloglide® group showed higher sensitivity scores at all, but especially at early visits.

Progression of Tinel's Sign

In regard to progression of the distance of Tinel's sign from the site of surgery, the analysis performed when the sign was present showed that the distance from the site of surgery at day 30 was significantly longer in the Hyaloglide®-treated group (mean, 1.07 cm in treatment arm vs. 0.38 cm in controls; $P = 0.042$) (Table 3).

DISCUSSION

Hyaloglide® is an absorbable barrier based on autocrosslinked HA in a gel-based form. It is highly biocompatible and has increased in situ residency times compared to native, unmodified HA. These properties may make its use feasible for circumventing postsurgical adhesions following surgical repair of peripheral nerve lesions. To directly assess this possibility, we investigated the safety, tolerability, applicability, and efficacy of Hyaloglide® gel following microsurgical suture or neurolysis of peripheral nerves of the hand in a controlled, randomized trial. A total of 30 subjects, including 14 in the treatment group and 16 in the control group, underwent clinical evaluation.

Several important points can be concluded from the present clinical trial. First, no safety concerns were raised and no adverse effects on either wound closure or nerve repair were observed at follow-up visits in either treatment group, and the applicability of hyaloglide was judged as favorable in all cases. Second, the percent improvement of pain, assessed as the change from pain at baseline to no pain at postsurgical visits, appeared more favorable in the treatment group, especially during the first 3 months post-

Table 2. Recovery of Sensitivity in Hyaloglide and Control Patients at Various Follow-Up Visits

Follow-up	Hyaloglide	Control	*P*
Day 10	($N = 12$)	($N = 15$)	
S-0	1 (8)	2 (13)	0.731
S-1	1 (8)	1 (7)	
S-2	0 (0)	3 (20)	
S-3	3 (25)	3 (20)	
S-3+	5 (42)	5 (33)	
S-4	2 (17)	1 (7)	
Day 30	$N = 12$	$N = 15$	
S-0	0 (0)	1 (7)	0.725
S-1	2 (17)	1 (7)	
S-2	1 (8)	2 (13)	
S-3	2 (17)	4 (27)	
S-3+	4 (33)	6 (40)	
S-4	3 (25)	1 (7)	
Day 60	$N = 12$	$N = 16$	
S-0	0 (0)	1 (6)	0.237
S-1	2 (17)	0 (0)	
S-2	0 (0)	3 (19)	
S-3	3 (25)	5 (31)	
S-3+	2 (17)	4 (25)	
S-4	5 (42)	3 (19)	
Day 90	$N = 12$	$N = 16$	
S-0	0 (0)	1 (6)	0.267
S-1	2 (17)	0 (0)	
S-2	0 (0)	1 (6)	
S-3	2 (17)	7 (44)	
S-3+	3 (25)	3 (19)	
S-4	5 (42)	4 (25)	
Day 180	$N = 12$	$N = 16$	
S-0	0 (0)	1 (6)	0.398
S-1	2 (17)	0 (0)	
S-2	0 (0)	1 (6)	
S-3	2 (17)	6 (38)	
S-3+	2 (17)	3 (19)	
S-4	6 (50)	5 (31)	
Day 360	$N = 12$	$N = 16$	
S-1	2 (17)	1 (6)	0.408
S-2	1 (8)	1 (6)	
S-3	1 (8)	5 (31)	
S-3+	2 (17)	5 (31)	
S-4	6 (50)	4 (25)	

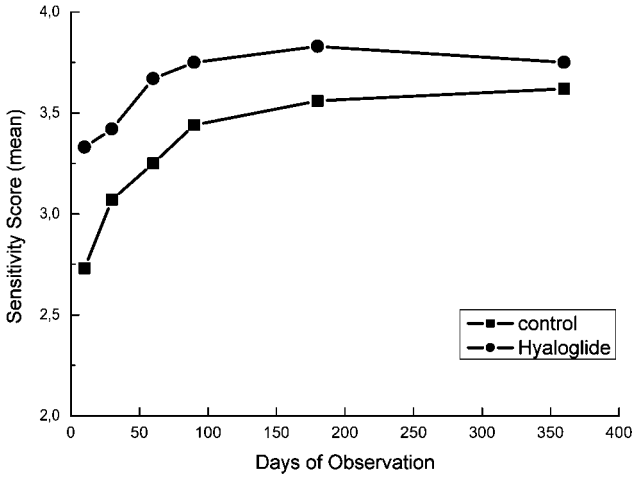

Figure 3. Mean sensitivity scores during follow-up in the hyaloglide-treated and control groups. Scores were calculated using the following scheme: S0, 0; S1, 1; S2, 2; S3, 3; S3+, 4; S4, 5.

Table 3. Postsurgical Assessment of Tinel Sign at Follow-Up Visits[a]

Days	*N*	Mean ± SD	*P*[b]
10			
Control	7	0.27 ± 0.47	0.195
Hyaloglide	11	0.79 ± 0.91	
30			
Control	7	0.38 ± 0.48	0.042
Hyaloglide	12	1.07 ± 0.73	
60			
Control	7	1.96 ± 2.69	0.849
Hyaloglide	14	1.13 ± 0.87	
90			
Control	7	2.46 ± 3.12	0.91
Hyaloglide	14	1.57 ± 0.93	
180			
Control	7	2.43 ± 3.27	1.000
Hyaloglide	14	1.14 ± 0.85	
360			
Control	7	1.71 ± 2.49	0.848
Hyaloglide	14	1.02 ± 0.76	

[a]*The distance from the lesions was measured in cm. Only patients with a positive Tinel sign were included.*
[b]*Wilcoxon's test.*

surgery. Moreover, the improvement in the degree of pain was more pronounced in Hyaloglide®-treated group compared to the control group during the postsurgical period and approached statistical significance at days 30 ($P = 0.055$) and 60 ($P = 0.060$). With regard to the distance of Tinel's sign from the site of surgery, the analysis performed when Tinel's sign was present showed than the distance at day 30 was longer in the Hyaloglide®-treated group (mean, 1.07 cm in treatment group vs. 0.38 cm in controls; $P = 0.042$). No statistically significant differences were observed in the distribution of recovery scores in the 2 groups at the end of the observational period, although the percentage of full recovery of sensibility (recovery class S-4) was higher in the Hyaloglide®-treated group at all postsurgery visits. Last, recovery of motor function was similar in the 2 groups.

Failure to restore peripheral nerve function after acute laceration or chronic compression may result in the loss of muscle function, impaired sensation, and additional neuropathies. Formation of restrictive perineural adhesions is one of the most common complications in peripheral nerve surgery. When a nerve is tethered to its adjacent bed by excessive perineural scaring, limitations in normal gliding cause mechanically-induced inflammation, leading to a chronic irritation of the nerve itself and interfering with migration of axons. It may also affect the outcome of surgery due to the onset of severe neuralgic pain and dysesthesiae, as well as cause delayed restoration of nerve function.

Numerous technical solutions have been both proposed and tested to overcome the problems of scarring. These include microsurgical techniques, endoscopic techniques, nerve transposition, dermofascial fat grafts, vein wrapping, and muscle flaps.[18] Nonetheless, the most efficient strategy for increasing the success of interventional procedures involving repair of peripheral nerve lesions remains high quality surgical practice accompanied by correct rehabilitation.

Recently, a similar product containing crosslinked HA molecules (Hyalobarrier gel) was demonstrated to be efficient in reducing adhesions in gynecologic and intra-abdominal surgery in both experimental and clinical trials.[10–14] This information suggests that a similar strategy could also be successfully applied to the prevention of adhesions in other types of surgical intervention including surgery of peripheral nerve lesions. Hyaloglide® may have dual effects in minimizing postsurgical adhesions by biological means as well as by acting as a reabsorbable barrier. The favorable biological effects on healing may be similar to that of native HA as a component of the extracellular matrix and synovial fluid.[6,9,19,20] Moreover, the high viscosity of the gel also reduces perineural adherence by separating surrounding tissues adjacent to the nerve.[15,16] The gel-based format also provides several advantages, including its easy of use, and, importantly, does not require removal. In addition, its elevated biocompatibility and prolonged residence times are compatible with healing, as it resides for a time sufficient to reduce adhesion formation before its degradation.

Several studies in animal models have shown that hyaluronate enhances regeneration of peripheral nerves in vivo. Human amniotic fluid, which contains high concentrations of HA, was found to enhance peripheral nerve regeneration and to have a preventive effect on epineural scarring when applied to the repair site in rats.[22] Moreover, when treated with HA, similar benefits to healing were observed in the rat model and better conduction velocities and faster recovery were observed in addition to a significant reduction in scar thickness.[2,21] The reduced scar for-

mation in the presence of HA after neurolysis was also confirmed in a rabbit model.[23]

Taken together, these experimental models are highly suggestive that HA would be effective in improving healing in microsurgical suture of peripheral nerves and likely point to Hyaloglide® as a valid strategy for surgical applications involving peripheral nerve regeneration.

The present clinical trial mainly substantiates previous cited experimental studies using HA for preventing adhesion and improving recovery after nerve surgery. Overall, recovery appeared to be more rapid in patients when Hyaloglide® was applied, and a trend of better restoration of sensitivity was seen throughout the lengthy observation period. To our knowledge, this is the first clinical study examining the safety and efficacy of hyaluronate-based gels in microsurgery of nerves. While statistical significance between the 2 treatment groups was, for the most part, not reached, this, in part, may be due to the limited number of cases studied. Last of all, it must be stressed that, while the choice of the nerves of the hand is ideal for the study of microsurgical adherences, it nonetheless renders interpretation of results difficult, due to the limited power of objective parameters to be evaluated.

CONCLUSION

The application of Hyaloglide® may improve recovery of sensitivity and pain following microsurgical repair of peripheral nerves by limiting formation of perineural adhesions and favoring regeneration of nervous tissue, creating a more favorable environment for the healing of the lesion. These initially encouraging results should be confirmed by larger studies.

REFERENCES

1. Wilgis EF, Murphy R. The significance of longitudinal excursion in peripheral nerves. Hand Clin 1986;2:761–766.
2. Ozgenel GY. Effects of hyaluronic acid on peripheral nerve scarring and regeneration in rats. Microsurgery 2003;23:575–581.
3. Adanali G, Verdi M, Tuncel A, Erdogan B, Kargi E. Effects of hyaluronic acid-carboxymethylcellulose membrane on extraneural adhesion formation and peripheral nerve regeneration. J Reconstr Microsurg 2003;19:29–36.
4. Mensitieri M, Ambrosio L, Nicolais L, Bellini D, O'Regan M. Viscoelastic properties modulation of a novel autocrosslinked hyaluronic acid polymer. J Mater Sci Mater Med 1996;7:695–698.
5. Toole BP. Hyaluronan in morphogenesis. Semin Cell Dev Biol 2001;12:79–87.
6. Zhong SP, Campoccia D, Doherty PJ, Williams RL, Benedetti L, Williams DF. Biodegradation of hyaluronic acid derivatives by hyaluronidase. Biomaterials 1994;15:359–365.
7. Renier D, Bellato P, Bellini D, Pavesio A, Pressato D, Borrione A. Pharmacokinetic behavior of ACP gel, an autocrosslinked hyaluronan derivative, after intraperitoneal administration. Biomaterials 2005;26:5368–5374.
8. Chen WY, Abatangelo G. Functions of hyaluronan in wound repair. Wound Repair Regen 1999;7:79–89.
9. Fraser JRE, Brown TJ, Laurent TC. Catabolism of hyaluronan. In: Laurent TC, editor. The Chemistry, Biology and Medical Applications of Hyaluronan and Its Derivatives. London: Portland Press; 1998. pp 345–449.
10. Acunzo G, Guida M, Pellicano M, Tommaselli GA, Di Spiezio Sardo A, Bifulco G, Cirillo D, Taylor A, Nappi C. Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: A prospective, randomized, controlled study. Hum Reprod 2003;18:1918–1921.
11. Belluco C, Meggiolaro F, Pressato D, Pavesio A, Bigon E, Dona M, Forlin M, Nitti D, Lise M. Prevention of postsurgical adhesions with an autocrosslinked hyaluronan derivative gel. J Surg Res 2001;100:217–221.
12. De Iaco PA, Muzzupapa G, Bigon E, Pressato D, Dona M, Pavesio A, Bovicelli L. Efficacy of a hyaluronan derivative gel in postsurgical adhesion prevention in the presence of inadequate hemostasis. Surgery 2001;130:60–64.
13. De Iaco PA, Stefanetti M, Pressato D, Piana S, Dona M, Pavesio A, Bovicelli L. A novel hyaluronan-based gel in laparoscopic adhesion prevention: Preclinical evaluation in an animal model. Fertil Steril 1998;69:318–323.
14. Pucciarelli S, Codello L, Rosato A, Del Bianco P, Vecchiato G, Lise M. Effect of antiadhesive agents on peritoneal carcinomatosis in an experimental model. Br J Surg 2003;90:66–71.
15. Dam-Hieu P, Lacroix C, Said G, Devanz P, Liu S, Tadie M. Reduction of postoperative perineural adhesions by Hyaloglide gel: An experimental study in the rat sciatic nerve. Neurosurgery 2005;56(2 Suppl):425–433; discussion 425–433.
16. Smit X, van Neck JW, Afoke A, Hovius SE. Reduction of neural adhesions by biodegradable autocrosslinked hyaluronic acid gel after injury of peripheral nerves: An experimental study. J Neurosurg 2004;101:648–652.
17. Shen N, Zhu J. Functional assessment of peripheral nerve injury and repair. J Reconstr Microsurg 1996;12:153–157.
18. Wilgis E. Clinical aspects of nerve gliding in the upper extremity. In: Hunter J, Schneider L, Mackin E, editors. Tendon and Nerve Surgery in the Hand. St. Louis: C.V. Mosby; 1997. pp 121–124.
19. Hagberg L. Exogenous hyaluronate as an adjunct in the prevention of adhesions after flexor tendon surgery: A controlled clinical trial. J Hand Surg [Am] 1992;17:132–136.
20. Laurent TC, Fraser JR. Hyaluronan. Faseb J 1992;6:2397–2404.
21. Burns JW, Skinner K, Colt J, Sheidlin A, Bronson R, Yaacobi Y, Goldberg EP. Prevention of tissue injury and postsurgical adhesions by precoating tissues with hyaluronic acid solutions. J Surg Res 1995;59:644–652.
22. Ozgenel GY, Filiz G. Effects of human amniotic fluid on peripheral nerve scarring and regeneration in rats. J Neurosurg 2003;98:371–377.
23. Ikeda K, Yamauchi D, Osamura N, Hagiwara N, Tomita K. Hyaluronic acid prevents peripheral nerve adhesion. Br J Plast Surg 2003;56:342–347.