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CASE REPORT

Hand/Peripheral Nerve

Nontubulation Repair of Peripheral Nerve Gap Using Heparin/Alginate Gel Combined with b-FGF

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Summary: All artificial nerve grafts have a tubular structure, and they guide axonal regrowth through the tube from the proximal side toward the peripheral side. Based on the results of our experimental study using animals, we used alginate gel without a tubular structure as an artificial nerve graft for digital nerve repair and evaluated peripheral nerve regeneration. In 2 patients, a gap due to digital nerve injury was bridged with controlled-release heparin/alginate gel combined with basic fibroblast growth factor, and restoration of the sensory function was serially evaluated. In both patients, Tinel's sign appeared 3–4 weeks after the operation, and sensory recovery to the fingertip was achieved at 6 months postoperatively. Our results suggest that even gel without a tubular structure provides a site for peripheral nerve regeneration. *(Plast Reconstr Surg Glob Open 2016;4:e600; doi: 10.1097/GOX.0000000000000581; Published online 27 January 2016.)*

All types of artificial nerve graft previously developed have a tubular structure. This tubular structure prevents fibroblasts with a high proliferative ability and surrounding fibrous tissue from entering the tube and secures the route of axonal elongation.[1,2]

However, we initiated a study aiming to elongate the axon from the proximal to distal stump of the gapped nerve using gel without a tubular structure and developed a alginate gel cross-linked with covalent bonds sterilized by cobalt 60 γ-radiation.[3,4] Restorations of the gap in cat sciatic nerve were obtained by using tubular or nontubular material consisting mainly of the alginate gel.[5] In addition, a heparin/alginate gel consisting of heparin and alginate covalently cross-linked with ethylenediamine was developed, which allowed the controlled release of b-FGF as a heparin-binding growth factor.[6]

Based on these results, we used the controlled-release heparin/alginate gel combined with b-FGF as an artificial nerve graft in patients with digital nerve injury with the approval of the Ethical Committee of Kitano Hospital.

CASE REPORT

Patient 1

A 57-year-old man accidentally severed his right thumb at zone III with an electric saw while working. We planned curing of the bone, tendons, arteries, and veins, followed by ulnar digital nerve repair. However, because general anesthesia was not used, he could not tolerate a prolonged operation, and the proximal stump of the nerve could be identified but not the distal stump. Therefore, we placed heparin/alginate gel combined with b-FGF between the proximal stump and tissue of the severed digit, expecting the axon itself to locate the distal nerve stump and regrow. The gap was greater than 7mm. Immediately after the operation, the moving 2-point discrimination (2PD) at

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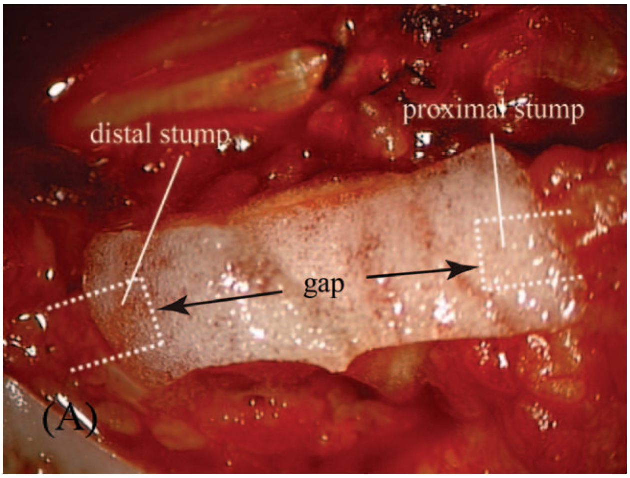

Fig. 1. Patient 2. Heparin/alginate gel combined with b-FGF was placed to bridge the nerve gap.

the fingertip was greater than 15 mm. Tinel's sign appeared 1 month after the operation. After 6 months, both the moving 2PD and static 2PD were 5 mm, and the value of the Semmes–Weinstein monofilament examination was 3.16.

Patient 2

A 51-year-old man fell while snowboarding and sustained a laceration to the right thumb in zone IV. After flexor tendon suturing, a 7-mm gap of the radial digital nerve was repaired with heparin/alginate gel combined with b-FGF (Fig. 1). Immediately after the operation, the moving 2PD at the radial fingertip was greater than 15 mm. Tinel's sign appeared 3 weeks after the operation. After 6 months, the static 2PD was 13 mm, and the value of the Semmes–Weinstein monofilament examination test was 3.16.

DISCUSSION

Nerve conduits made of collagen, polyglycolic acid,[7] or caprolactone have become commercially available as artificial nerve grafts, are widely used in clinical practice, and have achieved excellent results.[8] The tubular structure has been reported to prevent fibrous tissue infiltration and retain neurotrophic factors released from the damaged nerve ending in the tube.[2,9] However, these nerve tubes

Table 1. Problems of Artificial Nerve Tubes

Multiple nerve tubes differing in diameter should be prepared.
Tubes cannot be bent and can be used only for linear gap repair.
Tubes cannot be used for repair at branching sites.
Bioabsorbable materials should be used to prevent entrapment of the regenerated nerve.
When degradation and absorption are too rapid, the tubular structure collapses.
For suturing, microsurgical techniques are necessary, increasing the operative time.
Measures are necessary to supply adequate nutrients and oxygen required for nerve regeneration.

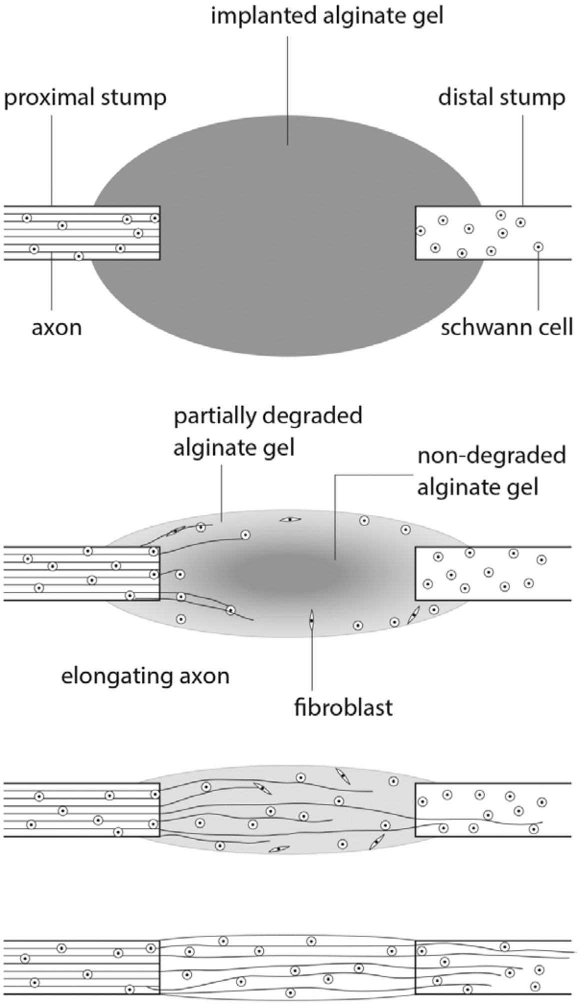

Fig. 2. Nerve regeneration mechanism of alginate gel. A, The gap of the peripheral nerve is bridged by alginate gel. B, The surface layer of the alginate gel that is in contact with the surrounding tissue is degraded first, resulting in low molecular-weight gel. Schwann cells migrate into the low molecular-weight gel from the proximal stump of the nerve, and the axon is elongated. From the distal stump, Schwann cells migrate. From the surrounding tissue, fibroblasts with a high proliferative ability also invade the gel. C, Degradation progresses to the gel center, and the axon from the proximal stump continues to grow and enters the distal stump, being led by Schwann cells that have migrated from the distal stump. Because a new site for axonal elongation is constantly provided due to gel degradation, the site for axonal elongation is not lost due to the proliferation of cells such as fibroblasts. D, After gel degradation and absorption, the regenerated nerve remains. Adapted with permission from Hashimoto T, Suzuki Y, Kitada M, et al. Peripheral nerve regeneration through alginate gel: analysis of early outgrowth and late increase in diameter of regenerating axons. *Exp Brain Res*. 2002;146:356–368.

have the associated problems shown in Table 1, and improvements have been made.

Alginate gel used as an artificial nerve graft has some advantages including nutrient absorption/retention by the spongy gel itself, applicability to nerves of all diameters and even for nonlinear gaps, and a reduction in the operative time due to no need for suturing. As shown by patient 1, detachment of the nerve stump from the surrounding tissue is not necessary, and the nerve can regrow as long as the stump is in contact with the gel. However, in both patients 1 and 2, Tinel's sign first appeared 3–4 weeks after the operation, suggesting delayed axonal elongation in the early stage. This may have been because alginate gel degradation was prolonged until the achievement of a state appropriate for axonal elongation from the proximal stump. In addition, there is a possibility that gel continuity is lost when the gel is used in mobile areas such as periarticular areas. The optimization of the degradation rate and an increase in the gel strength are requirements that remain to be realized (Fig. 2).

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