A novel technique leading to complete sensory and motor recovery across a long peripheral nerve gap

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Sensory nerve grafts are the "gold standard" for inducing neurological recovery in peripheral nerves with a gap. However, the effectiveness of sensory nerve grafts is variable, generally not leading to complete sensory and motor recovery, with good recovery limited to gaps shorter than 2 cm, and the extent of recovery decreasing with increasing graft length. An alternative technique using a conduit filled with pure fibrin to bridge a nerve gap leads to only limited neurological recovery. We tested the effectiveness of a novel nerve repair technique in which a 5-cm long radial nerve gap was repaired using two sural nerve graft surrounded by a collage tube filled with pure fibrin. By 1½ years post surgery, the patient recovered complete sensory and motor function. In conclusion, this study suggests that the combination of pure fibrin surrounding sural nerve grafts is responsible for inducing the extensive neurological recovery induced by either pure fibrin or sural grafts alone. This technique is presently being tested in a clinical trial.

Key words: Axon regeneration, Fibrin, Sural nerve graft.

The standard clinical technique for repairing a peripheral nerve gap when both ends can not be anastomosed is to bridge the gap with autologous nerve grafts harvested from the cutaneous saphenous or sural nerves (1-6). The assumption is that sensory nerve Schwann cell-released neurotropic factors and molecules in the nerve extracellular matrix should promote and direct axon regeneration across the nerve gap (7-12).

Sensory nerve grafts result in some neurological recovery in about 86% of patients with nerve gaps 1-5-cm in length, with generally limited recovery for gaps 1.5-2 cm in length, very limited recovery for gaps longer than 2 cm in length, and decreasing with further increases in gap length (4, 6, 10, 13-18). The reason for the limited recovery appears to be that the sensory axons use the sural nerve grafts as a passive scaffold across which the axons regenerate, rather than as an active regeneration-promoting pathway (4, 19, 20).

Vascularized sensory nerve grafts significantly improve the extent of neurological recovery compared to that induced by non-vascularized nerve grafts (21, 22). However, the far more extensive surgery required to prepare vascularized nerve grafts, significantly limits their general application.

Alternative methods for bridging nerve gaps are pseudo nerves, CNS tissue grafts, collagen guides, guides filled with neurotrophic factors, gradients of factors, antibodies, factors that induce inflammation, biodegradable polymer tubes, and filling tubes with various materials such as collagen or artificial fibrin matrix (5, 18, 23-35). However, most of these techniques fail to promote axon regeneration across gaps longer than 2 cm and provide no better neurological recovery than sural nerve grafts (35, 36). Therefore, sensory nerve grafts use remain the "gold standard" for the clinical repair of transected peripheral nerves (5, 37, 38).

Case Report

The present surgical repair was performed to determine whether a modification of the standard sural nerve graft technique might lead to more extensive neurological recovery than typically seen across a long radial nerve gap.

A 21-year-old male presented to the hospital two months after a traumatic radial nerve lesion at the elbow. Exposure of the injury site showed both nerve stumps to be inflamed (Figure 1A). After removing the damaged tissue, the nerve had a 5-cm long gap inflamed (Figure 1B). Two lengths of sural nerve were placed into the gap and sutured in place in accordance with standard surgical repair procedures inflamed (Figure 1C-D). A sheet of collagen (artificial dura, Duraguard, Synovis Corp. St. Paul, MN, USA) was sewn into a tube around the grafts, with a diameter slightly larger than that of the radial nerve inflamed. The ends of the

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radial nerve were inserted about 3 mm into the collagen tube, and the collagen tube was sewn to the epineurium of the ends of the radial nerve (Figure 1E). The space between the nerve grafts and tube was then filled with fibrin (cryoprecipitate) combined with thrombin. This combination led to the polymerization of fibrinogen within the cryoprecipitate into a 3-dimensional matrix (Figure 1F).

By 1½ years post surgery, the patient showed no signs of muscle atrophy, had recovered complete motor and sensory function and suffers no pain related to the nerve injury and repair, and had had no adverse effects from the repair. The patient developed sensitivity to touch, temperature, pain, vibration and normal 2-point discrimination on the dorsal aspect of his hand, identical to that of his un-injured hand.

Motor recovery included full and graded wrist and finger extension, indicating the establishment of many motor units. The force exerted by the wrist and fingers was virtually identical to that of the uninjured hand, indicating full muscle innervation. Graded electrical stimulation of the radial nerve above the lesion site induced graded wrist and finger extension,

Evoked potentials were recorded when the radial nerve was stimulated from the thumb notch, forearm, elbow and above the elbow (at distances of 14-22 cm). The signal latency was normal at 0.2 ms, with an amplitude of 32 μv. Needle recordings from finger extensor muscles showed the muscles to be electrically silent during periods of muscle inactivity, and with no fibrillations. Voluntarily movement of selected fingers gave rise to normal evoked motor activity for the appropriate finger. These results indicate normal muscle innervation by the regenerated radial nerve axons and normal evoked action potentials.

The patient passed a rigorous military physical exam,

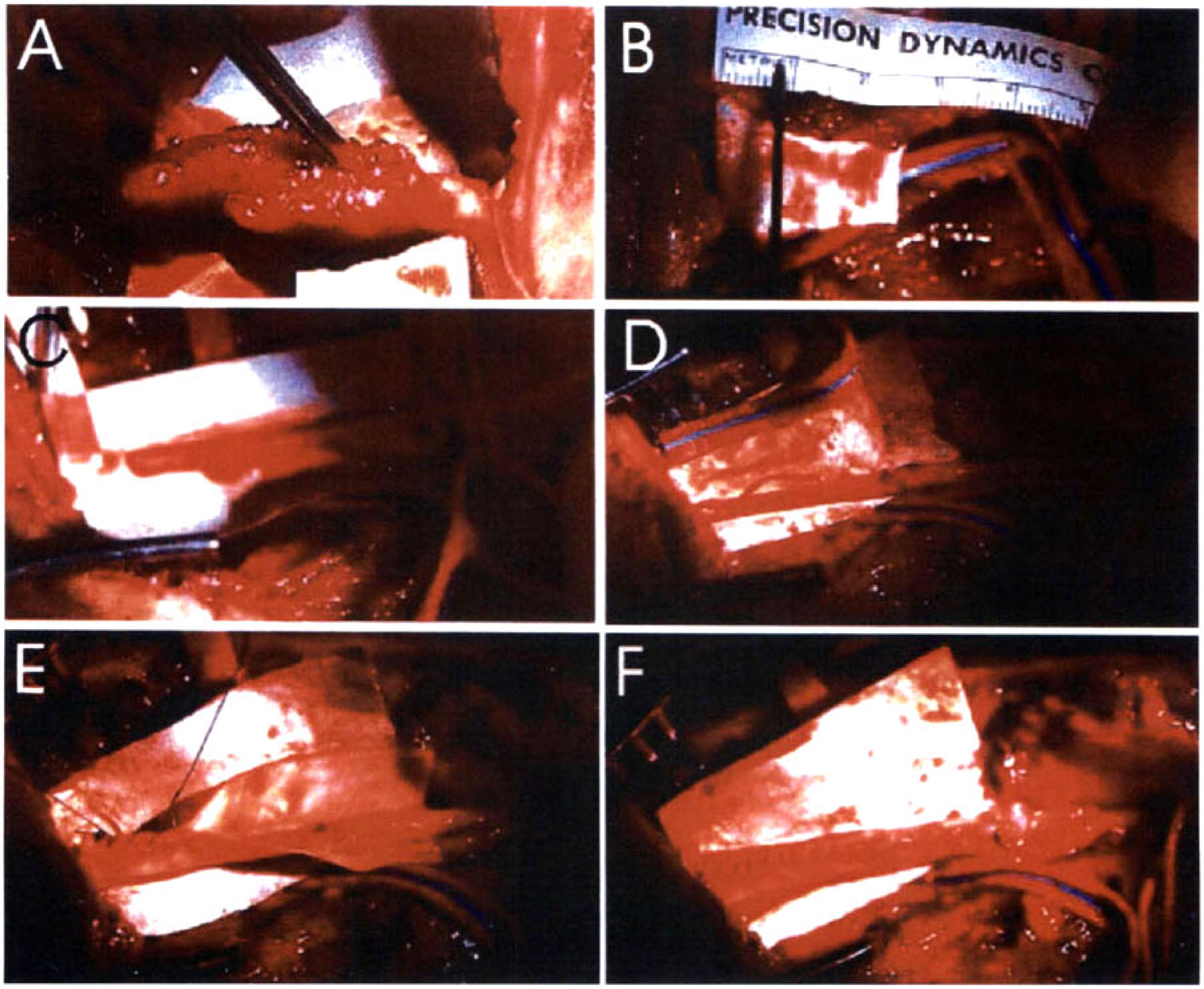

Figure 1. Photos of surgical repair procedures. A. Exposure of overlapping ends of transected radial nerve. B. Damaged nerve tissue from the proximal and distal stump are removed, resulting in a 5 cm gap. C. Positioning a length of sural nerve into the radial nerve gap. D. Two lengths of sural nerve grafted into radial nerve gap. E. Suturing a sheet of collagen around the sural nerve grafts. F. The complete nerve gap repair with the collagen tube filled with fibrin.

which concluded that he had no neurological deficits in the repaired hand. He enlisted and presently has a fulltime rigorous military job requiring full and equal use of both the repaired and un-injured hand.

Discussion

The aim of this study was to determine whether a new technique would induce more extensive neurological recovery across a 5-cm long radial nerve gap than typically induced cutaneous saphenous or sural nerve grafts. The repair involved using two sural nerve grafts surrounded by a collagen tube filled with pure fibrin.

The technique led to complete and normal motor and sensory neurological recovery that allows the patient identical use of both his repaired and un-operated hands. The observed complete sensory and motor recovery was more extensive than typically seen when sural nerve grafts are used alone to repair a nerve gap > 2 cm (16).

The study has several limitations. One is that as a case study the results are from only a single patient. Thus, further trials are required to determine the reliability of the technique in inducing neurological recovery. Another limitation is that the neurological recovery induced by sural nerve grafts is extremely variable. Therefore, it is important to consider that the observed recovery may fall within the variability of recovery induced by sural nerve grafts alone, although such complete recovery is not reported in the literature (16).

The literature indicates that good neurological recovery using only sural nerve grafts is limited to nerve gaps no longer than 2 cm in length, and that recovery decreases with increasing gap length (4, 6, 13, 16-18, 39). Further, the observed complete recovery is far greater than that seen by the surgeons involved in this study when they have repaired nerve gaps of 5-cm in length using only sural nerve grafts.

Pure fibrin within a conduit bridging a nerve gap induces neurological axon regeneration across short nerve gaps (4 mm) (40-42). However, axon regeneration is more extensive through fibrin when it is combined with trophic factors (34, 40, 43). Thus, the present data showing extensive neurological recovery most likely results from interactions of the fibrin with sural nerve-released factors.

It could be argued that tubulization of sural nerve grafts would inhibit ability to promote axon regeneration by causing the cells of the graft to become necrotic. However, the observed extensive neurological recovery indicates this is not the case.

A full clinical study is required to determine whether the nerve repair technique induces reliable neurological recovery, whether there is a maximum nerve gap length over which the technique is effective, and whether the technique restores neurological function when applied more than 10 months post trauma, the effective limit of sural nerve grafts.

In conclusion, this study suggests that the combination of pure fibrin surrounding sural nerve grafts enhances the extent of neurological recovery induced by either pure fibrin or sural nerve grafts alone.

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Resumen

Injertos de nervios sensoriales es el "estándar de oro" para reparar nervios prefiérales con una abertura para inducir recuperación neurológica. Sin embargo, la efectividad del injerto de nervio "sural" es variable, generalmente no conduciendo a una completa recuperación sensorial y motora, y buena recuperación esta generalmente limitada a aberturas más cortas que 2 cm, y disminuyendo según aumenta el largo de los injertos. Un conducto lleno de fibrina pura conectando una abertura nerviosa conduce a solo una recuperación neurológica limitada. Examinamos la efectividad de una novedosa técnica de recuperación nerviosa en la cual una abertura nerviosa radial de 5-cm fue reparada utilizando dos injertos de nervios "surales" rodeados por un tubo de colágeno lleno de fibrina pura. El paciente tuvo una completa recuperación sensorial y motora 1 año y medio después de la operación. Concluimos que la combinación de fibrina con el injerto de nervio "sural" es responsable de inducir una extensa recuperación neurológica. Estamos examinando la técnica en una prueba clínica.

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