Injury, Int. J. Care Injured xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Efficacy and safety of novel collagen conduits filled with collagen filaments to treat patients with peripheral nerve injury: A multicenter, controlled, open-label clinical trial

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ARTICLE INFO

Article history:
Accepted 12 March 2018

Keywords:
Artificial nerve conduit
Peripheral nerve injury
Collagen
Controlled trial
Open label

ABSTRACT

Introduction: The safety and efficacy of using artificial collagen nerve conduits filled with collagen filaments to treat nerve defects has not been fully studied in humans. We conducted a multicenter, controlled, open-label study to compare the safety and efficacy of artificial nerve conduit grafts with those of autologous nerve grafts.

Methods: We included patients with a sensory nerve defect of ≤30 mm, at the level of the wrist or a more distal location, with the first-line surgical methods selected according to a patient's preference. We compared sensory recovery using static two-point discrimination and adverse events between the artificial collagen nerve conduit and autologous nerve grafting.

Results: The artificial nerve conduit group included 49 patients, with a mean age of 42 years and nerve defect of 12.6 mm. The autologous nerve graft group included 7 patients, with historical data of an additional 31 patients, with a mean age of 36 years and nerve defect of 18.7 mm. The rate of recovery of sensory function at 12 months was 75% (36/49) for the artificial nerve conduit group and 73.7% (28/38) in the autologous nerve group. No serious adverse events directly associated with use of the artificial nerve conduit were identified.

Conclusions: The treatment of nerve defects ≤30 mm using artificial collagen nerve conduits was not inferior to treatment using autologous nerve grafts. Based on our data, the new artificial collagen nerve conduit can provide an alternative to autologous nerve for the treatment of peripheral nerve defects.

Introduction

Trauma and surgery, such as tumor resection, can cause peripheral nerve injury, with end-to-end nerve suturing or autologous nerve grafting performed to treat these injuries. If the nerve defect is too large for end-to-end suturing, an autologous nerve graft is selected. However, autologous nerve grafting requires that a normal nerve is sacrificed at a donor site. In order to avoid this, the feasibility of bridging the nerve defect with an artificial nerve conduit has been investigated.

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https://doi.org/10.1016/j.injury.2018.03.011
0020-1383/

The first artificial nerve conduits were generated using non-biodegradable materials, such as silicon. Although these nerve conduits do support peripheral nerve regeneration, there is a risk of entrapment between the silicon conduit and the regenerating nerve [1]. As such, the development and use of nerve conduits constructed with biodegradable materials have been investigated.

Artificial nerve conduits constructed using polyglycolic acid (PGA) have been successfully used in humans to bridge a digital nerve defect [2,3]. Artificial nerve conduits constructed using collagen and poly-L-lactic acid (PLLA) have also been used, with outcomes comparable to those of the standard reconstruction techniques [4,5].

Nerve regeneration can be enhanced by filling the nerve conduit with certain substances, rather than using a hollow conduit [6,7]. PGA–collagen conduits filled with laminin-coated collagen fibers have been investigated in animal models, with peripheral nerve regeneration confirmed by clinical observation, electrophysiologic testing, and histological evaluation at 12 months post-surgery [8]. Furthermore, a clinical study using artificial PGA–collagen conduits filled with collagen sponges was performed in humans, with good recovery of sensory function and improvement of pain having been reported [9].

As collagen possesses a higher biocompatibility and cellular affinity than synthetic polymers [10], Nipro (United States patent US 6953482 B2) has developed an artificial nerve conduit that is constructed using only collagen, consisting an outer collagen cylinder and longitudinal collagen filaments (Fig. 1). A study of these collagen nerve conduits in female Beagle dogs provided a detailed assessment of the process of morphological, electrophysiological and functional recovery of the regenerated nerves [11]. Although the efficacy and safety of artificial collagen nerve conduits have been confirmed in animal experiments, the efficacy and safety in humans remain uncertain. Therefore, we conducted a multicenter, controlled, open-label clinical study to investigate the efficacy and safety of artificial collagen nerve conduits in patients with sensory nerve injury, at the level of the wrist or more distal location, and compared outcomes to those obtained for patients who underwent autologous nerve grafting.

Materials and methods

Collagen conduits filled with collagen filaments

Enzyme-solubilized collagen (a mixture of collagen types I and III) was dissolved in water to prepare an aqueous solution and extruded in a coagulating liquid to produce the collagen filaments used to fill the conduits. The outer cylinder of the conduit was formed by wrapping collagen fiber around a mandrel, with the cylinder subsequently filled with the aqueous solution containing longitudinally aligned collagen fibers. The constructs were frozen and then lyophilized in vacuo. The construct contained 10% v/v of collagen filaments under dry conditions. The product was sterilized with gamma ray irradiation.

The artificial collagen nerve conduit has passed several tests for safety, including: genotoxicity, carcinogenicity, and reproductive toxicity tests (ISO10993-3); in vitro tests of cytotoxicity (ISO10993-5) and effect after implantation (ISO10993-6); as well as testing for irritation, skin sensitization(ISO10993-10), and systemic toxicity (ISO10993-11).

Study design and patient population

A multi-center, controlled, open-label study was performed in 9 facilities in Japan, between February 2010 and September 2014. This study was approved by the institutional review board of each institution. Patients with open or closed traumatic injuries involving sensory nerves at the level of the wrist, or more distal lesions, were candidates for inclusion in this study, according to the following inclusion criteria: age, 20–64 years at the time of surgery; provision of written informed consent, including a statement that they agreed to participate in this clinical study at their own will; injuries consisting of a completely divided peripheral nerve, classified as a neurotmesis according to Seddon's

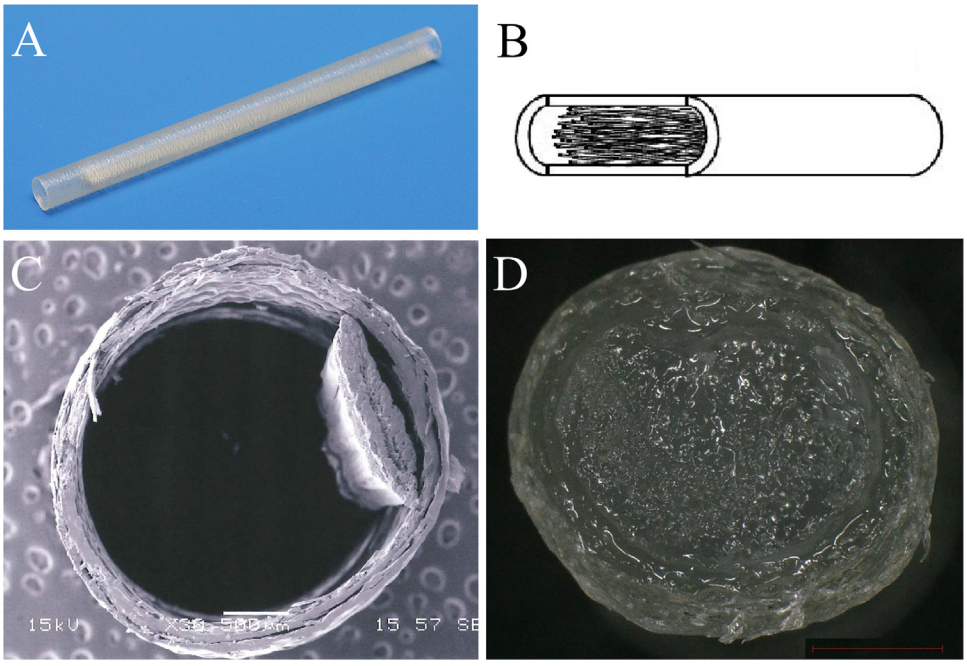

Fig. 1. The artificial nerve conduit.
A: Gross view of the artificial collagen nerve conduit filled with collagen filaments. B: Schema of the artificial collagen nerve conduit and collagen filaments. C: Electron microscope image of the collagen outer cylinder and collagen filaments (Dry state). Scale bar = 500 μm. D: Optical microscope image of the collagen outer cylinder and collagen filaments (Wet state). The outer cylinder was filled with the expanded wet filaments. Scale bar = 1 mm.

Please cite this article in press as: M. Saeki, et al., Efficacy and safety of novel collagen conduits filled with collagen filaments to treat patients with peripheral nerve injury: A multicenter, controlled, open-label clinical trial, Injury (2018), https://doi.org/10.1016/j.injury.2018.03.011