

Suzuki K<sup>1</sup>, Ukimura O<sup>1</sup>, Ushijima S<sup>1</sup>, Hirahara N<sup>1</sup>, Iwata T<sup>1</sup>, Honjo H<sup>1</sup>, Itoh T<sup>2</sup>, Hagiwara A<sup>2</sup>, Nakamura T<sup>3</sup>, Miki T<sup>1</sup>

1. Kyoto Prefectural University of Medicine, 2. Department of Digestive Surgery, Kyoto Prefectural University of Medicine, 3. Department of Bioartificial Organs, Institute for Frontier Medical Sciences, Kyoto University

## **HISTOLOGICAL AND ELECTROPHYSIOLOGICAL STUDY OF REGENERATION OF HYPOGASTRIC NERVE USING A POLYGLYCOLIC ACID (PGA)-COLLAGEN NERVE CONDUIT FILLED WITH COLLAGEN SPONGE IN CANINE MODELS**

### Hypothesis / aims of study

Restoration with sufficient functional recovery after nerve injury during surgery continues to be challenging. The hypogastric nerve (HGN) is a sympathetic nerve and controls urinary and seminal functions. Bilateral HGN and/or pelvic nerve complex are often excised in the surgeries of malignant tumors because of the local extension of the tumor or lymph node dissection. Although autonomic nerve preserving techniques have been attempted to avoid functional disturbance during such surgeries, the efficacy and indication are still limited. We have recently developed a new type of a biodegradable artificial nerve conduit, polyglycolic acid (PGA)-collagen nerve conduit filled with collagen sponge, and evaluated for peripheral nerve regeneration in animal model and patients (1-3). The aim of this study is to determine whether the gap of HGN was interposed with the aid of this new artificial nerve conduit, PGA-collagen nerve conduit filled with collagen sponge in a canine model. The nerve tissue reconnection through the nerve conduit was examined pathologically and the period of functional recovery was determined in electrophysiologically.

### Study design, materials and methods

Total sixteen adult male beagle dogs were used. The right HGN was cut with surgical scissors and a 10 mm long segment of HGN was removed. A PGA-collagen nerve conduit (tube with 2mm in diameter) with a length of 20 mm was interposed in the 10 mm gap. Each end of the tube was cut longitudinally 5 mm along the length of the conduit, and the proximal and distal nerve stumps end of the HGN were inserted into the opened part of the nerve conduit to a depth of 5mm (gap=10mm). The end of the stumps of the HGN was fixed to the conduit at the edge of the cut and the longitudinal cut lines were closed without suturing the nerve. Four dogs were sacrificed to confirm histological nerve extension through a PGA-nerve with toluidine blue stain and immunohistochemically at 2 weeks, 4 weeks, 6 weeks, and 8 weeks, respectively. Other twelve dogs were divided into 2 groups, the control group (n=2) and the implanted group (n=10) for electrophysiological study. The regeneration of the HGN was evaluated electrophysiologically 4 months (n=2), 5 months (n=2), 6 months (n=2), 7 months (n=2) and 8 months (n=2) after the operation, by stimulating the lumbar splanchnic nerves (LSNs) from L2 to L4 and measuring the response of the spermatic duct, bladder neck, and prostate. Before the nerve stimulation in all of the dogs, the left HGN was transected to eliminate the substitutive pathways.

### Results

Pathologically, at 2 weeks after implantation, the PGA-collagen tube was still macroscopically identified and the elongation of axons was observed from the proximal to distal end within the gap on specimens of toluidine blue staining. At 4 weeks, the implanted site was macroscopically replaced by connective tissues with histological increase of elongation of axons within the gap. At 8 weeks, the PGA-collagen tube disappeared, and nerve axons reconnected completely through the 10 mm gap. In the control, electrostimulation of the left LSNs induced elevation of intraluminal pressure of the spermatic duct (80 mmHg amplitude, and 10 seconds duration), elevation of bladder neck pressure (20mmHg amplitude), and prostate contraction (25 seconds duration). When the right HGN was transected after the measurement, no response was observed by the stimulation of the left LSNs (control). In the dogs with 4, 5, or 6 months follow-up, no response was observed by stimulation of the left LSNs. In the dogs with 7 months as well as 8 months follow-up, electrostimulation of left LSNs elicited elevation of intraluminal pressure of the spermatic duct (about 80mmHg, and 10

seconds), elevation of bladder neck pressure (about 25 mmHg, and 20 seconds), and prostate contraction (20 seconds). After the excision of the area of the interposed right HGN, no response was observed.

#### Interpretation of results

Our PGA-collagen nerve conduit can guide autonomic nerve elongation and lead to functional recovery through a 10 mm surgical gap of hypogastric nerve.

#### Concluding message

With the aid of a PGA-collagen nerve conduit filled with collagen sponge, the HGN could be regenerated through a 10mm gap during 1-2 months, followed by functional recovery with 7-8 months follow-up. The artificial nerve conduit has potential to be alternative to conventional autograft for the repair of autonomic nerve defects in retroperitoneal and pelvic surgery.