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A novel biodegradable device for intestinal lengthening

Veronica F. Sullins [a], Justin P. Wagner [a], Arnold T. Suwarnasarn [b], Steven L. Lee [a], Benjamin M. Wu [b], James C.Y. Dunn [a,b,*]

[a] Department of Surgery, Division of Pediatric Surgery, University of California, Los Angeles, Los Angeles, CA 90095–1749, USA
[b] Department of Bioengineering, University of California, Los Angeles, Los Angeles, CA 90095–7098, USA

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ABSTRACT

Purpose: Previous studies demonstrated successful mechanical lengthening of rat jejunum using an encapsulated Nitinol spring device over a stabilizing guidewire. We sought to improve the applicability of intestinal lengthening by creating a biodegradable device.

Methods: Using properties of the Nitinol spring device, polycaprolactone (PCL) springs with similar outer diameter and spring constant were created. After in vitro testing in dry and hydrated environments, they were used to lengthen 1-cm isolated segments of rat jejunum in vivo. Retrieved segments were analyzed histologically.

Results: Optimal PCL spring devices had an average spring constant 1.8 ± 0.4 N/m, pitch 1.55 ± 0.85 mm, and band width 0.825 ± 0.016 mm. In vitro testing demonstrated stable spring constants. Jejunal segments were lengthened from 1.0 cm to 2.7 ± 0.4 cm without needing a stabilizing guidewire. Histology demonstrated increased smooth muscle thickness and fewer ganglia compared to controls. Lengthened jejunum was successfully restored into intestinal continuity and demonstrated peristalsis under fluoroscopy.

Conclusions: A novel biodegradable spring device was successfully created and used to mechanically lengthen intestinal segments. Use of a biodegradable device may obviate the need for retrieval after lengthening. This improves device applicability and may be useful for the treatment of short bowel syndrome.

Short bowel syndrome (SBS) is a devastating condition owing to loss of significant intestinal length thereby affecting the organ's ability to absorb nutrients. This results in malnutrition, malabsorption and dehydration. The incidence of SBS is estimated to be 24.5 per 100,000 live births [1]. Despite improvements in medical and surgical management over the last few decades, mortality in the neonatal population has remained 20–40% [1,2]. The diagnosis of SBS is clinical, although it is typically associated with resection or loss of 70% or more of functional small intestine. Etiologies in the neonatal population include necrotizing enterocolitis, midgut volvulus, aganglionosis, intestinal atresias, abdominal wall defects and complicated meconium ileus [3]. While management strategies have changed significantly over the last few decades, morbidity owing to gastric hypersecretion, fluid and electrolyte abnormalities, osteoporosis, parenteral nutrition dependence, central venous catheter-related complications, and secondary hepatic dysfunction and failure remains high [3–6]. Even with a low prevalence in the pediatric population, health care costs are significant at an estimated $1.6M per patient [7]. Current surgical therapy includes transit-slowing and bowel lengthening procedures, and in the most severe cases small bowel and liver transplantation [3,8,9]. These procedures have significant complications [10], can only be performed in selected patients, and the 5-year survival rate of transplantation is 54% [11].

To address the fundamental issue of inadequate functional intestinal length in SBS, recent research has focused on distraction enterogenesis, a method of lengthening existing bowel. This concept has reached clinical success in multiple tissues including bone, breast, esophagus, urethra, and most recently in the aorta [12–16]. Multiple devices have been developed in recent years with encouraging results [17–21]. We previously showed that jejunum could be lengthened over 3-fold with an encapsulated Nitinol spring device and that this lengthened segment could successfully be restored into continuity [22,23]. In this model a stabilizing guidewire was necessary to prevent buckling of the spring during deployment. In addition, use of a non-biodegradable material may necessitate device retrieval if used in an endoscopic delivery system. We therefore sought to improve upon the applicability of the device by using a biodegradable material with the structural integrity to obviate the need for a stabilizing guidewire.

1. Materials and methods

Animal use was approved by the Animal Research Committee (Institutional Review Board Number 2002-037-22) and complied with all established institutional regulations. Adult female Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) were used.

* Corresponding author. Department of Surgery, Division of Pediatric Surgery, Department of Bioengineering, University of California, Los Angeles, MC709818, 10822 Le Conte Avenue, Los Angeles CA 90095. Tel.: +1 310 206 2429; fax: +1 310 206 1120.
E-mail address: Jdunn@mednet.ucla.edu (J.C.Y. Dunn).

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All materials were FDA approved for use in humans. Intestinal lengthening was achieved using springs made from polycaprolactone (PCL), a biodegradable polymer used in absorbable suture. PCL springs with a similar spring constant (1 N/m) and outer diameter (3.4 mm) to Nitinol springs were constructed. Springs were placed in cellulose acetate phthalate-coated (Eastman Chemicals, Kingsport, TN), size 5 gelatin capsules (Torpac Inc, Fairfield, NJ) for spring compression and delayed expansion. All operations were performed by a single surgeon.

1.1. Spring development

Polymer springs were fabricated using a 3.8% (w/w) PCL (Lactel, Birmingham, AL) solution in chloroform. PCL solutions were spray-coated onto a spinning 4 mm stainless steel mandrel to form polymer tubes with 300 and 500 μm radial thickness. Polymer spirals were hand cut from PCL tubes, elongated to 30 mm, and heat set at 50 °C for 1 hour to form final PCL springs (Fig. 1). Spring constants were measured using an Instron electromechanical testing system (Instron, Norwood, MA). The springs were tested in dry, hydrated and degraded conditions. Springs tested in dry conditions were measured in ambient air. Those tested in hydrated conditions were immersed in phosphate buffered saline (PBS) at 37 °C for 10 minutes prior to testing. Degraded PCL springs were incubated in 37 °C in PBS for 2 and 4 weeks then tested. Spring specifications producing spring constants most closely resembling previously used Nitinol springs were used to fabricate final springs. These were compressed into coated gelatin capsules as described above.

1.2. Surgical procedure

Rats were anesthetized with inhaled oxygen and isoflurane ($n = 5$). PCL spring devices were surgically placed into 1-cm isolated segments of jejunum approximately 10-cm from the ligament of Treitz as previously described [23]. Encapsulated 1-cm PCL tubes were placed into isolated jejunal segments to serve as controls ($n = 4$). Animals were explored 4–6 weeks postoperatively. After length measurements and tissue samples were collected, the lengthened segment was restored into continuity as previously described ($n = 4$) [24]. All animals survived. Of note, longer segments of jejunum from each end were sampled to obtain adequate tissue for histologic analysis. Thus, the restored segment length did not represent the total length of functional tissue. Animal weights were recorded weekly.

1.3. Radiographic evaluation

After the second procedure, animals underwent oral gavage with Omnipaque (GE Healthcare, Waukesha, WI) between 2 and 4 weeks. Small bowel follow through under fluoroscopy was performed with radiographs taken every 15 minutes until contrast was identified in the cecum. Gastrocecal transit times were recorded. Segments of restored jejunum were identified and visualized under fluoroscopy during the contrast study.

1.4. Histologic analysis

Normal and mechanically lengthened jejunal tissues were retrieved and fixed in 10% buffered formalin overnight. Tissue embedded in paraffin blocks was cut into 5 μm sections and stained with hematoxylin and eosin. Sections were viewed and recorded on a light microscope at 40× and 100× magnification. Thickness of the muscularis propria and circumference were measured. Unstained tissue sections were prepared and stained for S100 positive glial cells as previously described [25]. The number of ganglia was assessed at 100× magnification under fluorescent light microscopy in submucosal and myenteric plexuses and expressed as number of ganglia per mm circumference.

1.5. Statistical analysis

Data were expressed as mean values ± standard deviations. Two-tailed and paired Student's *t* tests were used for statistical analyses where appropriate.

2. Results

2.1. Spring development

After testing 300 and 500 μm thickness springs, the devices most closely approximating the forces of the Nitinol spring had an average spring constant of 1.8 ± 0.4 N/m, outer diameter 3.34 ± 0.075 mm, pitch (distance between coils) 1.55 ± 0.085 mm, thickness 293 ± 8.17 μm, and band width 0.825 ± 0.016 mm (Table 1). Spring constants remained unchanged after testing in dry, hydrated and degraded environments (Fig. 2).

2.2. Lengthening

Jejunal segments were lengthened from 1 cm to 2.7 ± 0.4 cm ($p < 0.001$), a nearly 3-fold increase (Fig. 3). Isolated jejunal controls containing encapsulated 1-cm PCL tubes expanded from 1 cm to 1.6 ± 0.2 cm ($p < 0.05$). The change in length between experimental and control groups was statistically significant ($p = 0.002$). Lengthened segments were successfully restored back into intestinal continuity (Fig. 4).

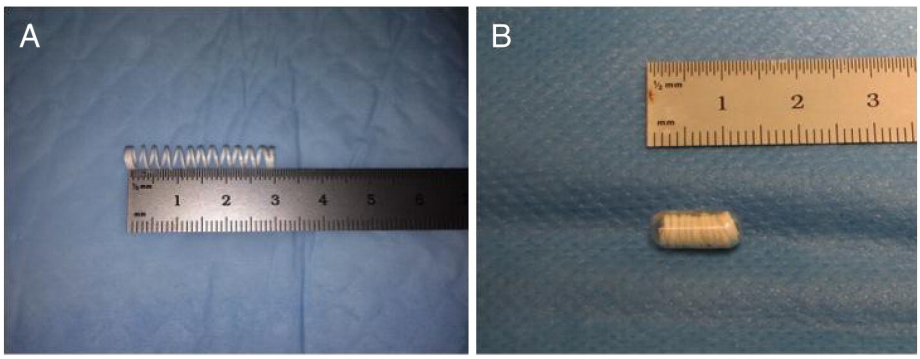

Fig. 1. (A) Expander PCL spring prior to encapsulation. (B) Encapsulated PCL spring prior to implantation.